EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

GLOBAL ATLAS OF PLANETARY HEALTH

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Setting the scene

Chemical pollution

The health impact

Prevention, adaptation and mitigation

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Editors

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Isabella Pali-Schöll

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FOREWORD

Human activities, primarily the burning of fossil fuels, widespread deforestation, soil erosion or machine-intensive farming methods, manufacturing, food processing, mining, construction, and the industries of iron, cement, steel, plastic and chemicals, have been the main drivers of the observed increase in Earth's average surface temperature and climate change. Rising global temperatures, extreme weather events, disruption of ecosystems, agricultural impacts, scarcity of water, problems in access to good quality water, food and housing, and profound environmental disruptions such as biodiversity loss and extreme pollution are expected to steeply increase the prevalence and severity of acute and chronic diseases. These environmental stressors alter the human exposome and trigger complex immune responses. In parallel, pollutants, allergens, and other environmental factors cause the disruption of skin and mucosal barriers and microbial dysbiosis, while a general loss of environmental biodiversity and microbial diversity in the body impairs tolerogenic immune response development. The resulting immune dysregulation is contributing to an increase in immune-mediated diseases such as asthma and other allergic diseases, autoimmune diseases, neuropsychiatric diseases and cancer. Studying the complex interaction between environmental aggressors and the resilient adaptive responses requires the exposomic and the One Health approaches. More than 300'000 new substances have been introduced to human lives after 1960s without any major concern on their effects to health and environment. Many of them have ended as pollutants. The problem is broad and affects the whole ecosystem, plants, pets, and animals in addition to humans. The central role of the epithelial barrier, microbiome, and diet as key pillars for an innate and adaptive tolerogenic immune response should be explored for increasing resilience at the individual level. A radical change in mindset worldwide, with sustainable solutions and adaptive strategies and climate resilience and health equity policies at their centre, should be achieved quickly through increased awareness based on solid scientific data.

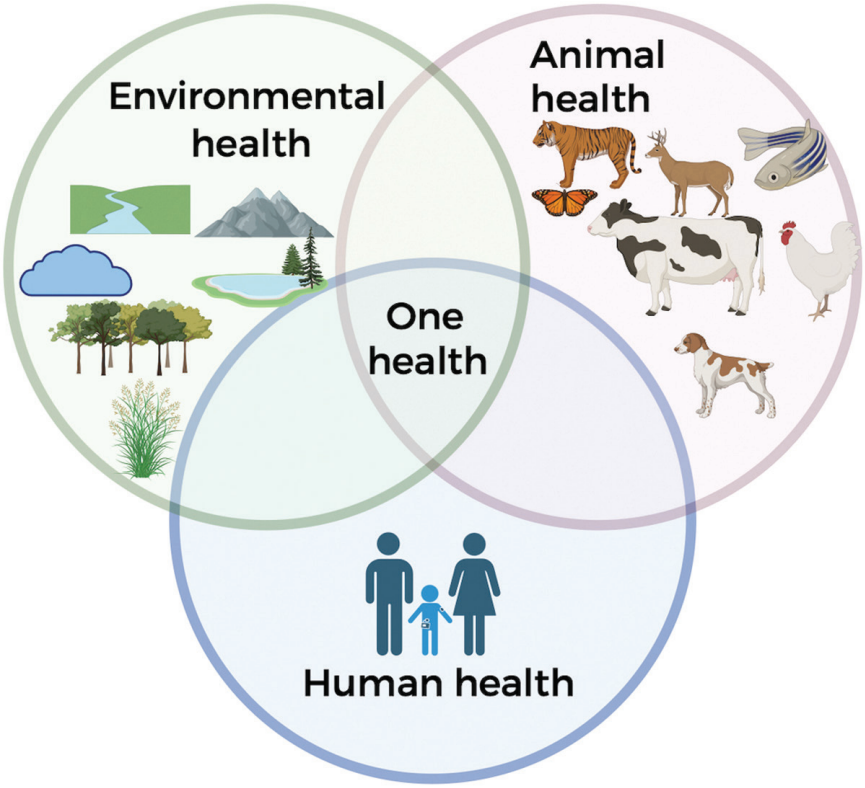
It is now abundantly clear that multi-sectoral, multidisciplinary, and transborder efforts based on Planetary Health and One Health approaches (which consider the dependence of human health on the environment and natural ecosystems) are urgently needed to adapt to and mitigate the effects of climate change. Key actions include reducing emissions and improving air quality (through reduced fossil fuel use), providing safe housing (e.g., improving weatherization), improving diets (i.e., quality and diversity) and agricultural practices, and increasing environmental biodiversity and green spaces. There is also a pressing need for collaborative, multidisciplinary research to better understand the pathophysiology of immune diseases in the context of climate change. New data science techniques, biomarkers, and economic models should be used to measure the impact of climate change on immune health and disease, to inform mitigation and adaptation efforts, and to evaluate their effectiveness. Justice, equity, diversity, and inclusion considerations should be integral to these efforts to address disparities in the impact of climate change.

This EAACI Global Atlas on Planetary Health brings together 50 international experts to describe both the direct and indirect health impacts of climate change within the international, economic, political, and environmental context. It contains chapters on Planetary Health and One Health, biodiversity loss, chemical pollution, the epithelial barrier defect, describes their health impact and provides guidance on prevention, adaptation and mitigation This unique Atlas also expands on longer-term impacts on global health: famine, population dislocation, and environmental justice and education. This scholarly resource explores these issues fully, linking them to global health in urban and rural settings in developed and developing countries. A practical discussion of action that health professionals, patients and citizens around the world in our field can yet take is included at the end. We are very glad that this Atlas is freely available to download and would like to thank all of the authors for their contributions.

Cezmi Akdis and Ioana Agache

Global Atlas of Planetary Health

Section A



SETTING THE SCENE

* Asthma, allergies and planetary health
* One health and planetary health
* Climate change
* Wars and military conflicts
* Biodiversity loss in human microbiome
* Explaining the changing patterns in health outcomes - the microbiome
* Biodiversity loss signs the allergy epidemic
* Respiratory viral infections
* Molecular mechanisms of epithelial barrier defect

1 ASTHMA, ALLERGIES AND PLANETARY HEALTH

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KEY MESSAGES

- The burden of ill-health from asthma and allergies may be increased by air pollution, climate change and land use change (including reforestation with allergenic species)
- The magnitude of the impacts on health vary by geographical location and socio-demographic characteristics of the population exposed, as well as by access to effect health care
- Actions to mitigate climate change (and other environmental changes) can yield near-term direct and indirect co-benefits for human health

There are several pathways and mechanisms by which global environmental changes and the driving forces causing these changes influence the burden of ill-health from asthma and allergies. Fossil fuels continue to represent 80% of the total energy supply and are also the major contributor to both greenhouse gas emissions causing climate change (particularly CO_2 and Methane, CH_4) and ambient air pollution, including from PM2.5, NO_2 and tropospheric ozone (O_3, for which methane is a precursor). Methane is also emitted from ruminants, rice paddies, gas leaks and other sources. Climate change may also exacerbate air pollution, for example because of increased risk of landscape fires. There is good evidence that exposure to air pollution from landscape fires increases risks of emergency room attendance and hospitalization with asthma.

Increasing temperatures influence the phenology, including the length of the pollen season, in various countries. Elevated carbon dioxide (CO_2) may also increase pollen production. In Japan for example, sugi-pollinosis is the commonest health problem affecting over 40% of the population. It is due to sensitization to Japanese cedar pollen following the planting of large numbers of trees in the post-war reforestation program. Exposure to Asian Dust arising from Mongolia and other dry locations in East Asia and urban particulate matter (PM) are risk factors for sugi-pollinosis. Hot summers generally promote flower bud development and increasing pollen production. The mean temperature in Japan has increased over several decades because of climate change.

Sensitization to ragweed is projected to more than double in Europe, from 33 to 77 million people, by 2041–2060, mainly because of climate change, with the greatest proportional increases predicted in countries where sensitization is currently uncommon (e.g., Germany, Poland, France). A study of consultations with primary care practitioners for allergic rhinitis in London showed that air pollution levels of SO_2 over 4 days preceding and O_3 levels over three preceding days and on the day of the consultation were highly significantly associated with increases in consultations, particularly in children, suggesting that exposure to these pollutants exacerbates allergic symptoms.

The relationship between asthma and air pollution has been extensively studied using both short -term and long-term exposure measurements. A systematic review of short-term exposures to ozone (O_3), nitrogen dioxide (NO_2) and sulphur dioxide (SO_2) and asthma exacerbations (indicated by emergen-

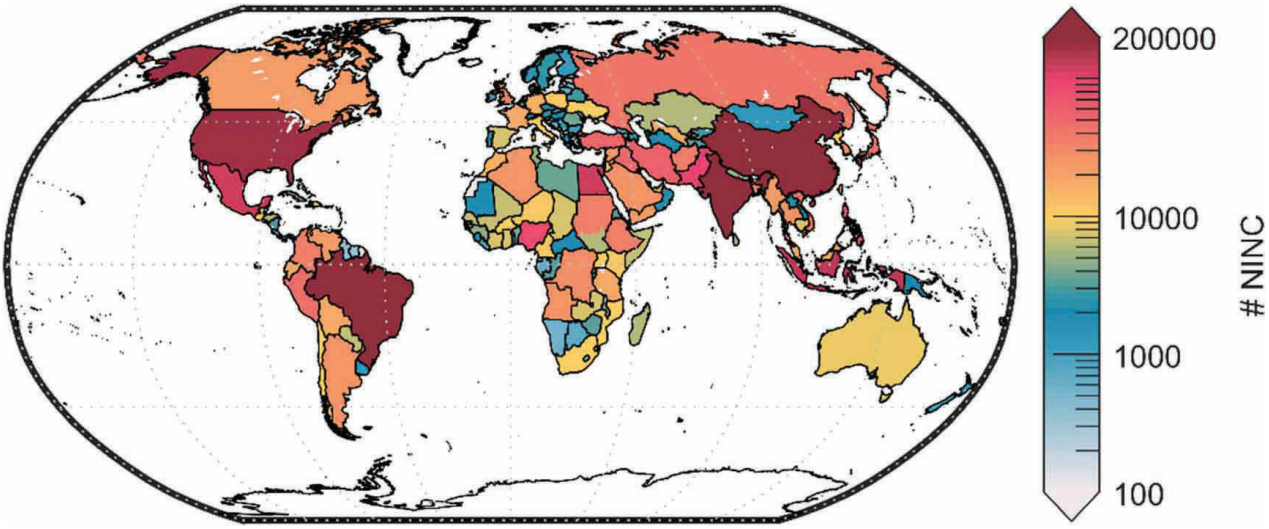

Figure 1 Incident cases of asthma among children and adolescents (NINC) per year attributed to exposure to ambient NO_2.

cy room visits (ERVs) and hospital admissions (HAs)), showed that the certainty of evidence (assessed by an adaptation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE)) was high for 8-hour or 24-hour O_3 and 24-hour NO_2 and moderate for 24-hour SO_2, 1-hour O_3, and 1-hour SO_2. Sulphur dioxide is a cooling aerosol, so reducing emissions will accelerate climate change unless accompanied by rapid reduction in greenhouse gas emissions, particularly short-lived climate pollutants such as CH_4.

A study of the effect of NO_2 air pollution exposure on incident cases of asthma, estimated 3.5 (2.1–6.0) million attributable cases among children and adolescents per year globally, representing about 14% of the total asthma incident cases in these age groups see Figure 1. Emissions from land transportation are the leading contributor globally to NO_2 (~44%), followed by the domestic burning of solid fuels (~10.3%) and power generation from fossil fuels (~8.7%) with wide variation by country in the sources.

The relationships between asthma, allergies (and many other health outcomes) and climate change underscore the need to accelerate progress towards universal access to clean renewable energy and more sustainable food and transport systems to reduce the risks of climate change and to capitalise on the near -term health co-benefits of climate action.

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2 ONE HEALTH AND PLANETARY HEALTH

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KEY MESSAGES

- Chronic non-communicable diseases such as asthma and allergies are increasing globally
- Rapid increases in the burning of fossil fuels and release of anthropogenic synthetic chemicals have caused increases of greenhouse gases levels and global warming with adverse effects on planetary and human health leading to increases in chronic non-communicable diseases
- The recognition that the health of people is connected to the environment has given rise to the concept of One Health, which aims to sustainably balance and optimize the health of people, animals and ecosystem

INTRODUCTION

Chronic, noncommunicable diseases such as allergies, autoimmune diseases, and cardiovascular diseases are becoming epidemic throughout the world. While genetics play a major role in the etiology of these diseases, the increases in the prevalence of these diseases are too rapid to be caused by genetics alone. A review of literature found geographical variability in the prevalence of allergic rhinitis worldwide in adults, however, most of the studies reviewed reported increases between 5-25% over the last decades. The increases in allergic diseases correlate with the rapid changes that have occurred in our environment since the start of the industrial age. The rapid increases in the burning of fossil fuels have led to increases in greenhouse gases (GHGs), global temperatures, frequency and intensity of wildfires and sand and dust storms leading to increases in air pollution, particularly particulate matter (PM). Higher temperatures and GHGs have increased pollen season length, concentration, and allergenicity. Increased manufacturing and release of synthetic chemicals into the atmosphere are polluting the air, water, and soil. Many of these chemicals are persistent organic pollutants, which persist in our environment and accumulate over time as they take hundreds to thousands of years to degrade. These environmental changes are decreasing the human health and the health of the planet as the two are inextricably linked.

Human beings are constantly being exposed to the environment they live in, and these exposures affect health. The measure of all the exposures that an individual is subjected to in a lifetime and how those exposures relate to health has been termed the exposome. These include both external and internal exposures such as chemicals, climate, fauna and flora, microbiome, diets and lifestyle. The recognition that the health of people is connected to the environment has given rise to the concept of One Health which is an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems. It takes a broad approach and involves partnerships and communication between research scientists, veterinarians, physicians, nurses, ecologists, policy makers, and others who work together to mitigate health threats.

Here, we discuss the various factors, such as PM, nitrogen oxides, ozone, volatile organic compounds, sulphur oxides, laundry

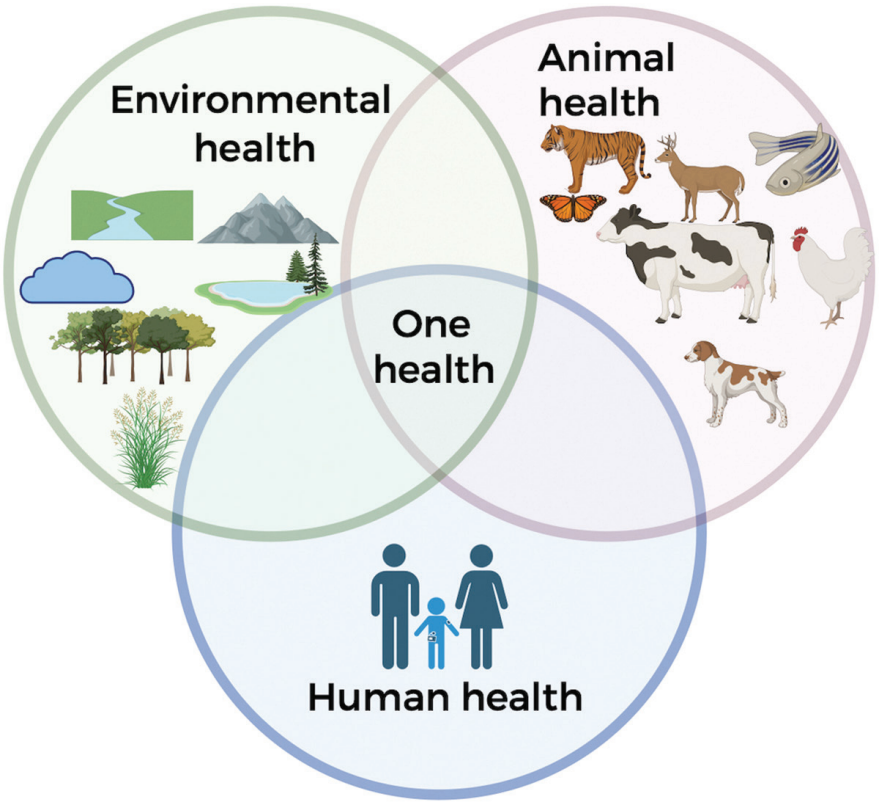

Figure 1 One Health is an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and the environment.

detergents, and food additives that are known to affect allergies and asthma and some of the mechanisms by which they do so. We discuss ways to prevent, adapt to and mitigate future increases in allergic diseases. Finally, how educators, health care workers, scientists, and others can promote One Health and Planetary health is discussed.

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3 CLIMATE CHANGE

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KEY MESSAGES

- Climate change is increasing the frequency and intensity of extreme weather events and wildfires and prolonging and intensifying the pollen season
- People with asthma and allergies, children and elderly, and historically marginalized and socioeconomically disadvantaged communities face disproportionate risks to their health from climate change
- There is an urgent need for developing and deploying mitigation and adaptation strategies in the near-term to build resilience and reduce exposure

INTRODUCTION

Greenhouse gas emissions warm the planet, leading to more frequent extreme weather events, such as floods, tropical cyclones, and heatwaves. Planetary warming is responsible for prolonging pollen seasons and creating conditions conducive to larger, more frequent wildfires. Exposure to extreme weather events, wildfire smoke, and pollen can exacerbate allergy and asthma symptoms. Every continent has been affected by climate change and extreme weather (Figure 1).

CURRENT AND FUTURE CLIMATE CHANGE EFFECTS ON ASTHMA AND ALLERGY

The 10 most recent years have been the warmest years on record with global temperatures 1.36°C above preindustrial levels and projected to rise by more than 2-4°C by the end of the century. Changes in climate directly and indirectly exacerbate allergies and asthma, both of which are significant contributors to the overall global burden of disease.

Warmer temperatures and precipitation promote pollen and mold growth, which are established triggers for asthma and allergies. Rain droplets fracture pollen grains into tiny granules that can be inhaled deep into the lungs. Climate change not only increases the within-season concentrations of pollen, but also prolongs pollen seasons. 2°C warming is projected to lead to additional allergy prescriptions, pediatric visits for allergic rhinitis, emergency visits for asthma annually. With 4°C warming, these impacts would nearly double.

While the effects of heat on mortality are more established, there is also evidence that higher temperatures and temperature variability may exacerbate asthma symptoms and deteriorate lung function. Heat promotes the formation of the air pollutant ozone, which is itself an established trigger for asthma. Ozone also increases the allergenicity of birch pollen by increasing *Bet v 1* allergen content in birch pollen grains and potentiating the immune response.

Smoke from wildfires contains particulate matter, a heterogenous mixture of particles and droplets, one of which is polycyclic aromatic hydrocarbon that has known immunologic effects. Wildfire smoke exposure can exacerbate asthma and atopic dermatitis and cause conjunctivitis and rhinitis, particularly in people with atopy.

Extreme weather events also disrupt access to healthcare. Communities are displaced from their homes, infrastructure is damaged, and hospital and clinics can shut down. Hurricanes in the US have

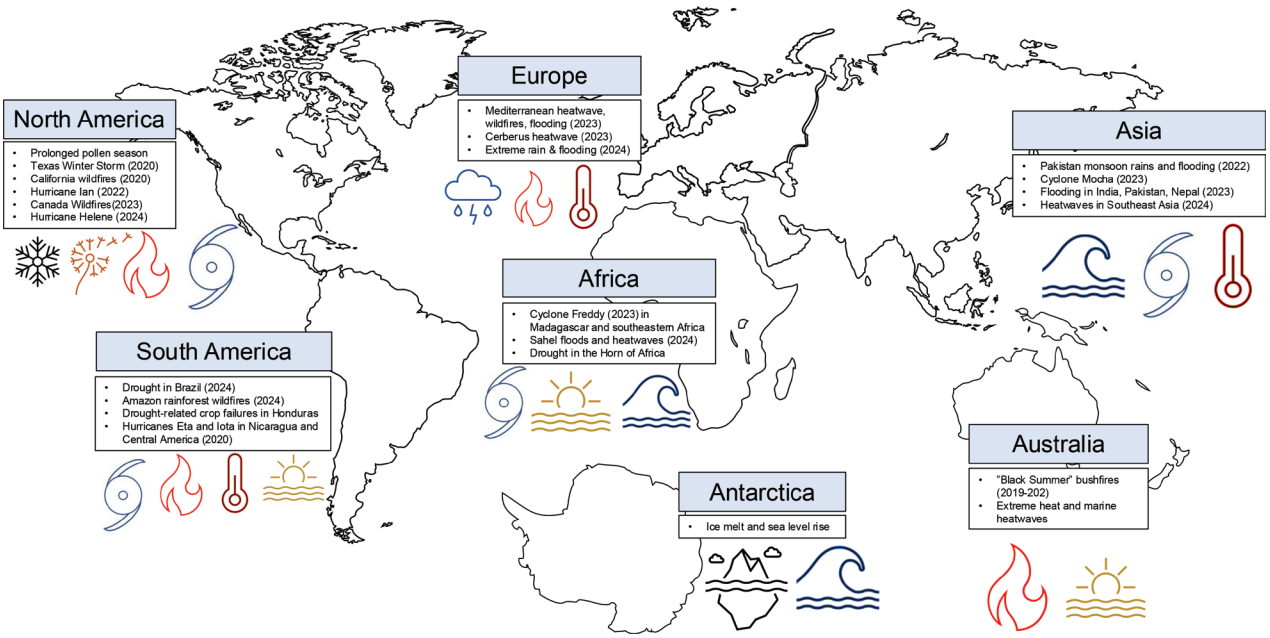

Figure 1 Selected recent extreme weather events across the globe. Climate change increases the frequency and intensity of extreme weather events, which can worsen asthma and allergy symptoms.

destroyed pharmaceutical manufacturing plants causing drug shortages, and forced hospitals to evacuate patients.

DISPARITIES IN EXPOSURE AND HEALTH OUTCOMES

Historically marginalized and socioeconomically disadvantaged communities face disproportionate risks to their health from climate change. The "climate gap" refers to disparities in exposure and health, with children, pregnant people, elderly, Indigenous populations, and low- and middle-income countries (LMICs) among the most vulnerable to climate change.

MITIGATION AND ADAPTATION STRATEGIES

As global temperatures continue to increase, effective mitigation strategies are needed to incentivize emissions reductions on a large scale. Simultaneously, adaptation strategies are required. Interventions like installing green roofs and expanding greenspace can lower temperatures indoors and decrease the urban heat island effect. However, other cooling interventions, such as air-conditioning, are not widely accessible and may exacerbate the urban heat island effect by transferring indoor heat outdoors and increasing air pollution from electricity generation. Further research is needed to develop and deploy interventions and measure effectiveness (Table 1).

CONCLUSION

Greenhouse gas emissions are causing extreme weather and climate events with well-established consequences for human health and accelerated biodiversity loss. Along with continued focus on reducing emissions, there is a need for advancing effective, cost-efficient adaptation strategies in the near-term to build resilience and reduce exposure.

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TABLE 1

Priorities for addressing climate change with respect to improving health outcomes in people living with allergies and asthma

Priorities	Examples
Reduce greenhouse gas emissions (mitigation)	1. Policy changes and incentives (e.g., carbon tax) 2. Electrification of vehicles and appliances 3. Consideration of emissions from land-use changes, such as deforestation
Develop evidence-based adaptation strategies	1. Community-based disaster response plans that involve historically marginalized people and Indigenous Peoples in decision-making 2. Effective early warning systems (e.g., cyclone warning systems) 3. Building design and materials (e.g., green roofs, ventilation, insulation) 4. Air cleaners (e.g., high-efficiency particulate air filters) and/or N95 masks for smoke and aeroallergens
Identify research priorities	1. Exposome and cumulative impacts (e.g., heat, pollen, air pollution) 2. Health disparities and characterization of climate exposures and health outcomes specifically in LMICs 3. Emerging health threats and interaction with heat/climate (e.g., microplastics, VOCs, PFAS) 4. Built environment (e.g., greenspace), indoor aeroallergens, and indoor air pollution
Promote education and awareness	1. Medical education, including structural determinants of health 2. Climate change implications for people with allergies and asthma 3. Individual actions to identify and reduce exposures to triggers for allergies and asthma 4. Translation of science to public and policymakers

4 WARS AND MILITARY CONFLICTS

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KEY MESSAGES

- Wars and military conflicts deplete natural resources, damage ecosystems and exacerbate climate change and deforestation
- They lead to health problems, involving increased disease spread, injuries, psychological stress as well as respiratory diseases, malnutrition, and many others
- Population displacement leads to overcrowding and increasing disease spread
- Destruction of public infrastructure hampers healthcare access, raising the risk of disease outbreaks
- Disruption of agricultural areas causes food insecurity and malnutrition
- Airborne hazards, which involve toxic chemicals and particulate matter, pose significant respiratory health risks

The multifaceted and far-reaching impact of wars and conflicts on planetary health was summarized in figures 1 and 2, which show the various ways and factors affecting the environment and human populations.

Wars and conflicts frequently result in the exploitation and depletion of natural resources such as timber, minerals, and fossil fuels. This damages ecosystems and exacerbates climate change and deforestation. Conflict forces millions to flee their homes, leading to overcrowding in refugee camps and immense pressure on resources in host countries. This can result in food and water shortages, poor sanitation, and disease spread, all significantly impacting public health.

Essential public health infrastructure, such as hospitals, clinics, and sanitation systems, is often targeted during conflicts, hampering healthcare access and increasing disease outbreak risks. Conflict disrupts agricultural activities, leading to crop failures, livestock losses, and disruptions in food distribution. This exacerbates food insecurity and malnutrition, particularly among vulnerable populations such as children, pregnant women, and the elderly. Chronic conflicts can hinder socioeconomic development and efforts to recover from environmental degradation, perpetuating poverty and vulnerability and further compromising planetary health.

Environmental degradation caused by military activity can hamper the resilience of ecosystems and human communities. For example, deforestation and habitat destruction increase regions' vulnerability to climate extremes and reduce ecosystems' capacity to sequester carbon, thus contributing to global warming.

During conflicts, various airborne hazards are released into the environment due to bombings, shelling, and infrastructure destruction. These hazards include particulate matter, toxic chemicals, heavy metals, and dust, posing significant respiratory health risks when inhaled (Table 1).

Moreover, the use of military materials like depleted uranium (DU) exerts significant environmental and health consequences. DU used during the Gulf War resulted in environmental contamination, with potential long-term health risks due to its chemical toxicity

Figure 1 War and chronic conflicts impact human health, including long-term effects.

Figure 2 War and chronic conflicts impact the environment and its degradation.

TABLE 1

The most common environmental degradation factors and their impacts during wars and conflicts

Harmful factor	Impact on environment	Impact on health and life
Enriched uranium	Long-term radiation contamination, soil, and water toxicity	Radiation exposure can lead to cancer, genetic damage, and other serious health issues
Depleted uranium	Radioactive contamination, health hazards, groundwater pollution	Similar to enriched uranium, can cause radiation sickness, cancer, and genetic mutations
Phosgene gas	Highly toxic, causes environmental toxicity	Causes severe respiratory damage, can be fatal upon exposure
Agent Orange	Dioxin contamination, deforestation, health impacts on humans and wildlife	Causes cancer, birth defects, and other serious health problems
White phosphorus	contamination of soil and water, long-lasting effects	Causes severe burns, organ damage, and can be fatal
Sarin, VX (nerve agents)	Extremely toxic, persistent environmental contamination	Lethal to humans and wildlife; inhibits acetylcholinesterase, leading to overstimulation of muscles and vital organs
Mustard gas	Persistent soil and water contamination	Causes severe blistering, respiratory problems, and can be fatal
Explosives residue (trinitrotoluene - TNT, Research Department eXplosive or cyclonite - RDX)	Toxic residues in soil and water, long-term environmental damage	Toxic, can cause cancer, liver damage, and other serious health issues
Chemical pollutants (polychlorinated biphenyls - PCBs)	Persistent organic pollutants, bioaccumulation, toxic to wildlife	Causes cancer, immune system damage, and other serious health effects
Heavy metals (lead, mercury)	Water and soil contamination, persistent environmental impact	Neurotoxic effects, can cause brain damage, kidney damage, and other serious health issues
Oil spills	Marine ecosystem damage, long-term shoreline contamination	Causes long-term health problems, including cancer and respiratory issues
Burn pits (large open-air pits used by the military to burn waste, releasing harmful pollutants into the air)	Release of toxic substances, air and soil contamination	Exposure to toxic substances can cause cancer, respiratory issues, and other health problems
Radiation (nuclear weapons)	Long-term environmental contamination e.g. soil, water, and vegetation for decades or even centuries; contamination affects the food chain, leading to bioaccumulation of radioactive materials in plants and animals; radioactive dust and particles can be dispersed over large areas, affecting air quality	Radiation exposure can cause cancer, acute radiation syndrome (radiation sickness); genetic mutations in plants and animals, leading to malformed offspring and decreased populations; and other serious health issues
Greenhouse gases (CO_2, methane)	Global warming, ocean acidification, climate change impacts	Contributes to respiratory problems (asthma, rhinitis, allergies), cardiovascular disease, and climate change-related health impacts
Particulate matter ($PM_{2.5}$, PM_{10})	Visibility reduction, ecosystem damage	Causes respiratory issues (asthma, rhinitis, allergies), cardiovascular problems, and can exacerbate existing health conditions.
Sulfur dioxide (SO_2)	Acid rain, damage to vegetation and water bodies (plants)	Causes respiratory problems, aggravates asthma
Nitrogen oxides (NOx)	Smog formation, damage to ecosystems	Causes respiratory issues, and can exacerbate heart conditions.

TABLE 1

continued

Harmful factor	Impact on environment	Impact on health and life
Carbon monoxide (CO)	Contributes to smog formation	Toxic to humans and animals, causes headaches, dizziness, and can be fatal at high concentrations
Volatile organic compounds (VOCs)	Air pollution, formation of secondary pollutants	Causes respiratory problems, can lead to long-term health issues
Pesticides and herbicides	Soil and water contamination, toxic to non-target species	Can cause cancer, neurological issues, and other serious health problems
Plastic debris	Marine and terrestrial ecosystem damage	Ingestion by wildlife can lead to death, and microplastics can enter the human food chain, causing health problems
Microplastics	Persistent in the environment	Persistent in the environment, ingestion by marine life can lead to contamination of the food chain, affecting human health
Asbestos	Persistent in the environment, soil and water contamination	Carcinogenic, can cause lung cancer, mesothelioma, and other serious health issues
Polycyclic aromatic hydrocarbons (PAHs)	Persistent environmental pollutants, bioaccumulation	Carcinogenic can cause lung cancer and other serious health issues
Dioxins	Highly toxic, persistent environmental pollutants, bioaccumulation	Highly toxic, can cause cancer, reproductive issues, and immune system damage
Furans	Highly toxic, persistent environmental pollutants, bioaccumulation	Highly toxic, can cause cancer, reproductive issues, and immune system damage
Ground-level ozone (O_3)	Damage to crops, ecosystem imbalances	Causes respiratory problems, exacerbates asthma, and damages lung tissue
Chlorofluorocarbons (CFCs)	Depletes ozone layer, increases UV radiation, causes climate change	Increases risk of skin cancer and cataracts due to higher UV radiation exposure
Hydrofluorocarbons (HFCs)	Global warming potential, air pollution	Causing indirect health impacts such as heat stress and food insecurity
Perfluorocarbons (PFCs)	Global warming potential, persistent in the atmosphere	Contributes to global warming, causing indirect health impacts such as heat stress and food insecurity.
Black carbon	Climate change, visibility reduction	Causes respiratory problems, cardiovascular issues
Methane hydrate release	Accelerates climate change, releases methane	Impacting global health and disruption of marine ecosystems
Mercury emissions	Contamination of water bodies and fish	Neurotoxic, can cause brain damage and affects kidney function
Lead-based paint	Soil and water contamination	health hazards, lead poisoning causes neurological damage, developmental delays in children, and other serious health problems
Mining waste	Heavy metal and toxic chemical contamination, habitat destruction	Can cause cancer, neurological damage, and other health issues
Industrial discharge	Chemical contamination of water affects aquatic life	Can cause cancer, reproductive issues, and other serious health problems
Eutrophication agents (phosphates, nitrates)	Algal blooms, oxygen depletion, water quality degradation	Causes algal blooms, which produce toxins harmful to human health and aquatic life
Landfill leachate	Toxic chemical leaching, groundwater contamination	Can contaminate drinking water, causing various health issues
Sewage overflows	Environmental pollution	Waterborne diseases from sewage overflows can cause serious illnesses such as cholera and hepatitis

and radioactivity, including cancer and kidney damage.

Conflict-related activities such as burning fossil fuels, building destruction, and industrial facility disruption contribute to air pollution. This pollution exacerbates respiratory conditions such as asthma, chronic obstructive pulmonary disease, and bronchitis, increasing the risk of respiratory infections.

The use of chemical weapons can severely impact respiratory health. Exposure to agents like chlorine gas, mustard gas, and nerve agents causes immediate respiratory distress, lung damage, and long-term health effects. Chronic exposure to airborne pollutants and environmental contaminants leads to chronic respiratory diseases, decreased lung function, and increased susceptibility to respiratory infections.

Conflict-induced displacement often results in overcrowded living conditions in refugee camps and informal settlements. These unsanitary environments increase the risk of respiratory infections such as influenza, tuberculosis, and pneumonia due to close contact and poor ventilation. Children bear substantial morbidity and mortality. Living in conflict-affected areas can result in significant psychological stress and mental health disorders such as anxiety, depression, and post-traumatic stress disorder.

Addressing the intertwined issues of planetary health, wars, and chronic conflicts requires comprehensive strategies integrating environmental conservation, sustainable resource management, and peace-building efforts. By acknowledging and mitigating the environmental impacts of conflicts, we can better protect biodiversity, ecosystem services, and human health in the face of ongoing and future challenges.

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5 BIODIVERSITY LOSS IN HUMAN MICROBIOME

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KEY MESSAGES

- Diet, environmental exposures, antibiotic use and human hygiene all play a role in the diversity of the human microbiome
- The loss of human microbial diversity plays a key role in the development of allergic disease, including food allergy, asthma, and atopic dermatitis
- Climate change exacerbates the loss of microbial diversity, which requires individual, community and policy level engagement to address
- Further research is needed to understand how our microbiomes influence immune health and to identify methods to maximize their beneficial effects

Recent literature has strongly implicated human microbiomes, specifically within the lung, gut and skin in the regulation and development of the human immune system. The biodiversity hypothesis states that contact with natural environments enriches the human microbiome, promotes immune balance, and protects from allergy and inflammatory disorders. Microbiome interactions between the gut, skin and lung, described as the gut-skin axis and gut-lung axis, indicate that changes in one form of microbiota can influence another. Development of a diverse internal microbiome is facilitated by human interaction with microbial diversity in the environment, for example through soil, water, plants and animals. Unfortunately, due to a variety of cultural and social implications, humans' interaction with diverse microbial diversity is declining (Figure 1). This loss in biodiversity has been amplified due to the effects of climate change and global warming.

There is increasing evidence linking microbial diversity and the dysbiosis of the human microbiome to a variety of different health conditions, including allergies and autoimmune diseases. Studies have found that individuals with allergic disease, including food allergies, asthma and atopic dermatitis have markedly lower levels of microbial richness compared to those that do not have allergic disease. Additionally, certain microbes have been linked to increased or decreased allergic disease susceptibility. For example, an increase in gut Bacteroides and a decrease in Clostridial species has been associated with peanut and tree nut allergies.

Further research is needed to fully understand the effects of the human microbiome on the immune system. Specifically, a focus should be on disproportionately impacted individuals, such as vulnerable and marginalized populations like those of low socio-economic status, children and people living with disabilities. As we better understand how the various environmental and social factors influence our microbiome, specific attention should be made to ensure vulnerable communities are not further marginalized.

As we continue to better understand the implications of the human microbiome, steps should be made to reduce human biodiversity loss. This involves considering not just in humans, but the environment as well. We must recognize the role climate change plays and address it at individual, community and policy levels. This

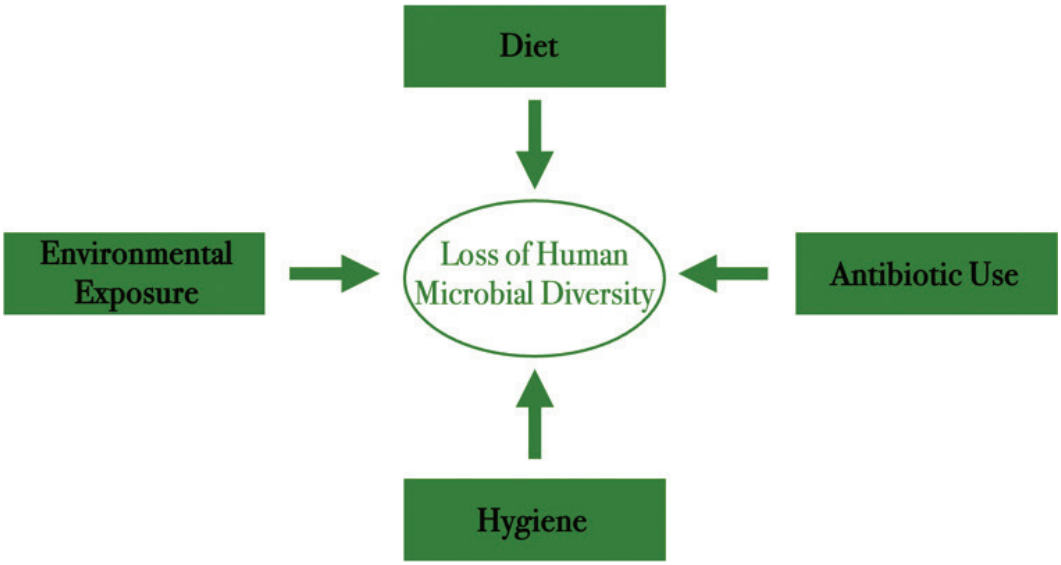

Figure 1 General categories affecting human microbial diversity.

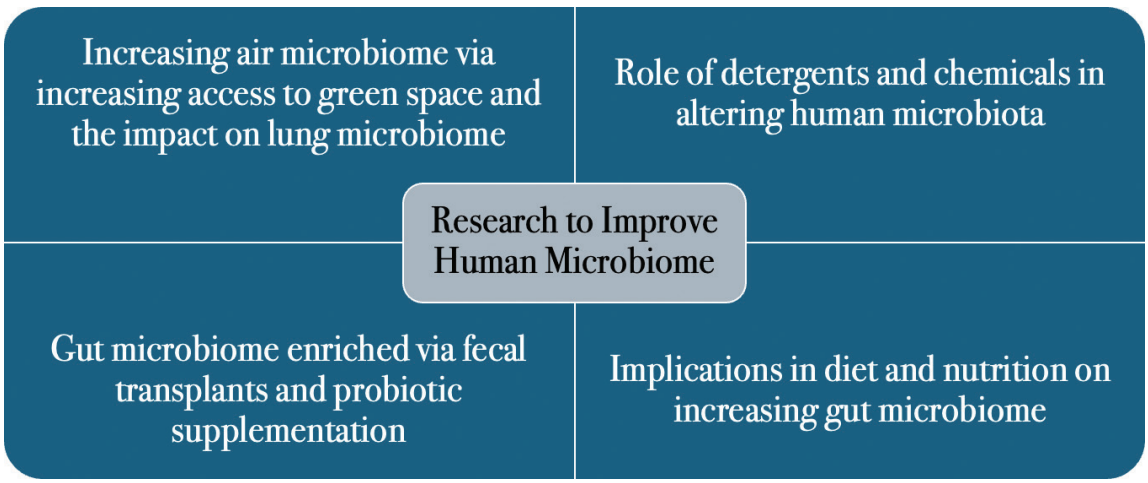

Figure 2 Summary of current research topics aimed at improving human microbial diversity and decreasing the negative immune effects of microbiota dysbiosis.

ultimately will help prevent the loss of human microbial diversity. Alternatively, methods to improve one's microbiome is an ongoing area of research (Figure 2). Identifying ways to decrease biodiversity loss among the human microbiome, is an important aspect of understanding, preventing and treating immunological disease.

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6 EXPLAINING THE CHANGING PATTERNS IN HEALTH OUTCOMES - THE MICROBIOME

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KEY MESSAGES

- The composition and function of gut microbiota, alterations in the host's immune status, and non-communicable, chronic inflammatory diseases are functionally connected
- Climate change can destabilize the microbiome and exacerbate the spread of pathogenic parasites, bacteria, fungi and viruses
- Future mitigating strategies should target both the environment and the microbiota

Allergic disease prevalence in urban populations is on the rise world-wide. This alarming phenomen is likely linked to environmental influences that alter the development and function of trillions of microbes inhabiting the human body (the microbiota) and their genes (the microbiome). Microbes and the immune system are intimately intertwined. Exposure to a diverse microbial environment during pregnancy shapes both microbiota and immune function in the mother. The pioneer microbes vertically transmitted from the mother colonize body habitats and shape immune function in the newborn, controlling the quality and quantity of environmental microbes that accumulate into these habitats in early life (Figure 1). The nascent gut microbiome then integrates dietary and pharmacologic encounters that affect microbiome membership, development and productivity, and gut microbial products influence immune function both locally and at remote mucosal sites. The combination of these processes shapes the trajectory along which microbiota and immune responses develop and ultimately affects allergic disease risk.

Lineages of gut microbes have co-speciated with humans over millions of years and hundreds of thousands of generations, suggesting that our microbial residents have shaped our biology throughout evolution. However, measures recently adopted to kill or limit exposure to pathogenic microbes (e.g., antibiotics and sanitation), combined with factors such as processed food diets and infant formula, have had unintended consequences for the human microbial ecosystem (Figure 2) and are now disturbing microbiome and immune development. Individuals who still follow traditional lifestyles around the world share strikingly similar microbiota composition profiles. In contrast, the configuration of microbiota harbored by individuals living in the industrialized world is one never before experienced by human populations. Relative to the "traditional" microbiota, the "industrial" gut microbiota has lower microbial diversity, with major shifts in microbiome membership and functions and increases in fast-growing microbes and often multi-resistant pathogens. Individuals immigrating from non-industrialized to industrialized settings or living at different intermediate states between foraging and industrialization have microbiota composition alterations that correspond to the time and severity of lifestyle change. Most importantly, more and more connections are emerging between the composition and function of the gut microbiota, alterations in the host's immune status, and multiple non-communicable, chronic inflammatory diseases. These connections appear to be mediated

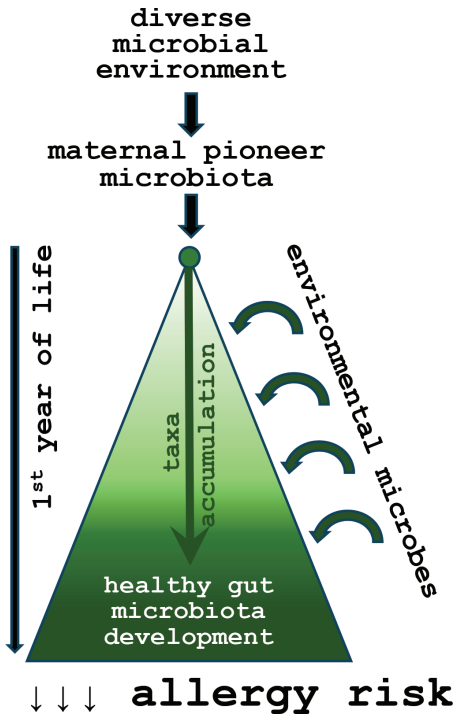


Figure 1 Interactions between environmental and gut microbiota influence microbiome development and allergic disease risk. *(Modified from Vercelli D. From Amish farm dust to bacterial lysates: The long and winding road to protection from allergic disease. Semin Immunol 2023;68:101779)*

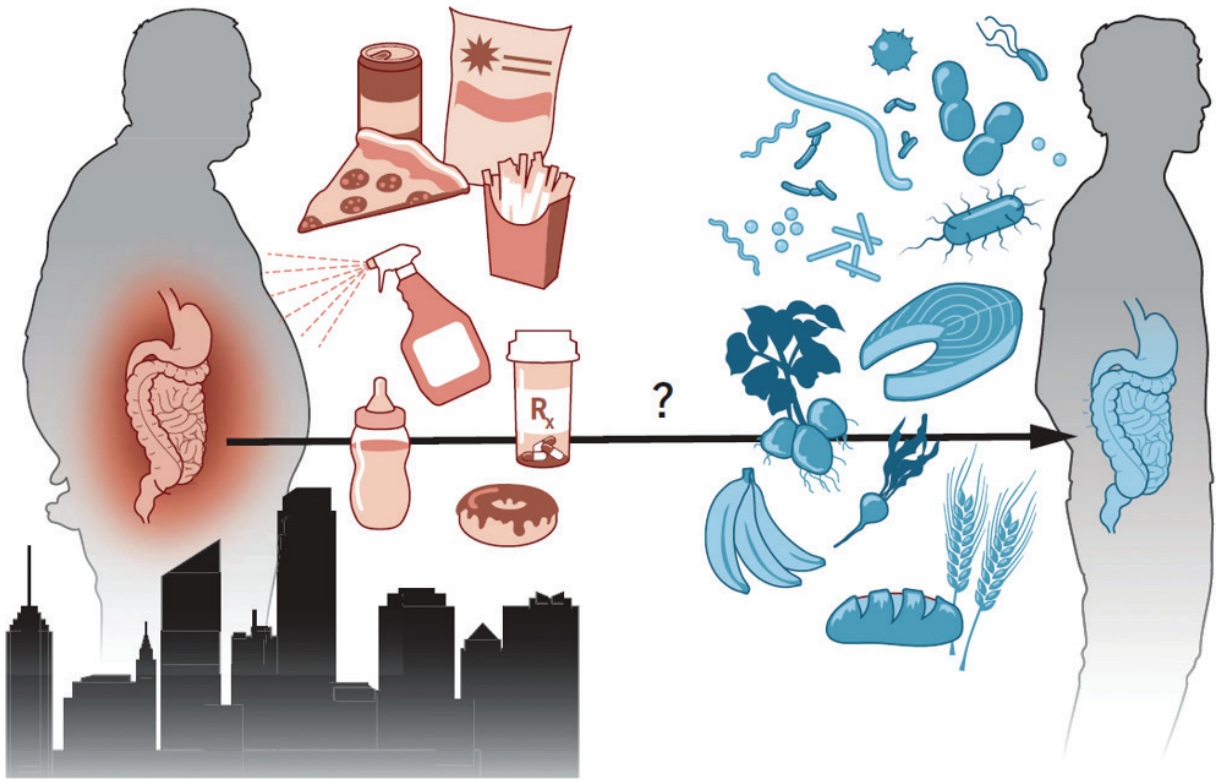
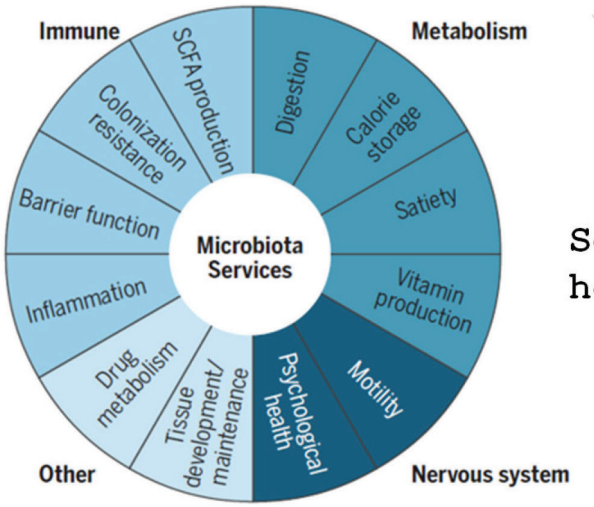
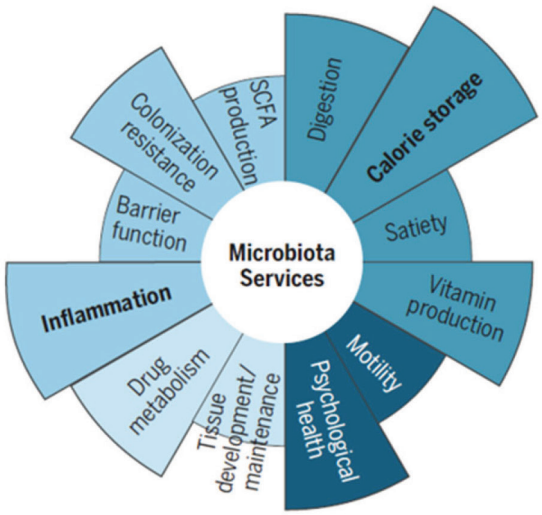


Figure 2 How an industrialized lifestyle may affect human gut microbiota. *(Modified from Sonnenburg JL, Sonnenburg ED. Vulnerability of the industrialized microbiota. Science 2019;366:eaaw9255)*



Services provided by healthy gut microbiota



Services out of balance in industrialized microbiota

Figure 3 Ecosystem services provided by human gut microbiota. *(Modified from Sonnenburg JL, Sonnenburg ED. Vulnerability of the industrialized microbiota. Science 2019;366:eaaw9255)*

through dysbiosis, a profound disruption of microbial networks and functions that facilitates disease by affecting the symbiotic relationships among microbiota and between the microbiota and their host. Because innate immunity and mucosal epithelial barriers are primary targets of dysbiosis, and their integrity is critical for the regulation of type-2 immune responses, these events can directly impact allergic disease pathogenesis.

Climate change can also destabilize the microbiome and exacerbate the spread of pathogenic parasites, bacteria, fungi and viruses. Extreme weather events, air pollution, heat waves, wildfires and deforestation pave the way for outbreaks of vector-borne diseases and trigger the emergence of pathogenic traits in previously benign microbial species (e.g., fungi). Moreover, these events can affect the food chain supply and feeding habits. The net outcome of these changes is a reduced contact of people with natural environments and a loss of environmental biodiversity that impairs the development of both the microbiome and the immune system of human hosts.

Future mitigating strategies should target both the environment and the microbiota. Identifying medical, diet, and sanitation approaches that are mindful of

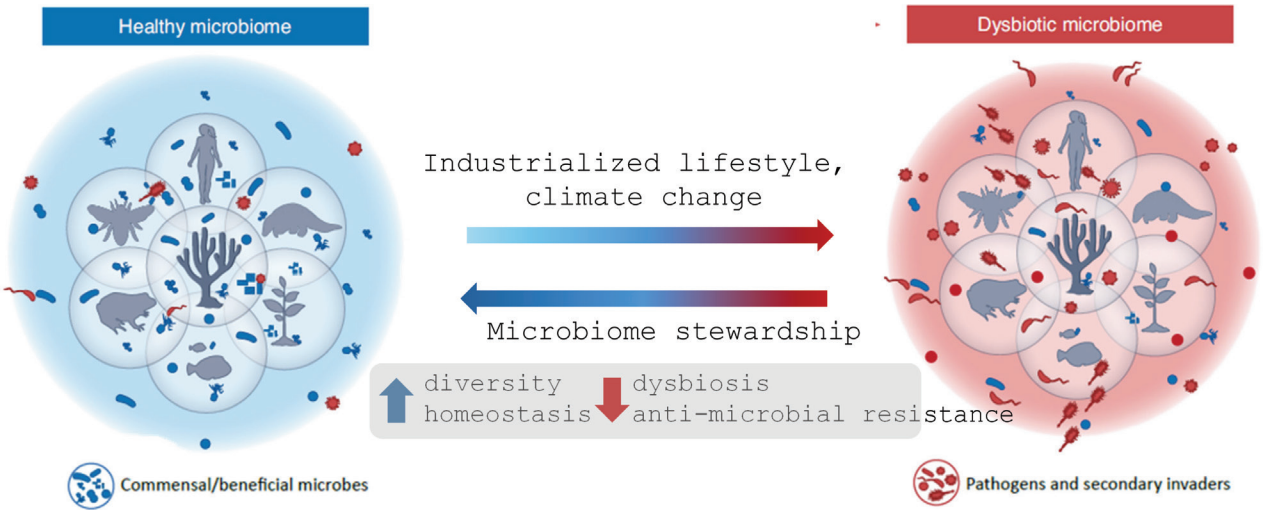


Figure 4 Microbiome stewardship as a potential tool to restore microbiome composition and function altered by industrialized lifestyles and climate change. *(Modified from Peixoto RS, Voolstra CR, Sweet M, Duarte CM, Carvalho S, Villela H, et al. Harnessing the microbiome to prevent global biodiversity loss. Nat Microbiol 2022;7:1726-1735)*

the importance and vulnerability of microbiota may promote a sustainable relationship with our internal microbial world. At the same time, isolating and archiving bacterial strains that are sensitive to industrialization may help preserve ecosystem services that are unique to those strains and potentially beneficial to human health (Figure 3) – a "microbiome stewardship" based on a careful and responsible management of the microbiome and aimed at rehabilitating organisms and ecosystem functions (Figure 4).

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7 BIODIVERSITY LOSS SIGNS THE ALLERGY EPIDEMIC

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KEY MESSAGES

- Biodiversity loss takes place not only in the wider ecosystems but also in the ecosystem of the human body
- Urban changes in the environment and lifestyle are the main causes of the allergy epidemic indicating a general increase of non-communicable diseases
- Diagnosing and managing nature deficiency become part of clinical practice along with new biomarkers and evidence from interventions
- Biodiversity hypothesis of allergy and health in general integrates public health promotion and environmental care

Biodiversity is fundamental for all life on earth. It means biological variety among ecosystems, species, genes, and cultures. This variety ensures stability and resilience also for humans in diverse conditions. Biological mechanisms include e.g., functional redundancy, broader utilization of available resources, and weak among species interactions. Population explosion, human dominance, urbanization, and increasing use of natural resources have reduced biodiversity not only in the wider nature but also in the ecosystem of the human body (Figure 1).

URBAN LIVING FOR BETTER LIFE

The urban progress and innovations have remarkably improved standard of living and reduced many *risk factors* for health and life expectancy. At the same time, however, *protective factors* have declined along with modern lifestyle endangering the immune regulatory circuits. Connection of the human body to natural air, soil, and waters – to our evolutionary home – has weakened (Figure 2).

In the Russian Karelia, hay fever, food allergy, and type 1 diabetes were almost non-existent in children. Small-scale agricultural and self-contained lifestyle, close to nature, trained the immune system to make a difference between danger and non-danger or self and non-self. The contrast between the Russian and Finnish Karelia was mainly explained by the richness and diversity of the microbiome. The well-known allergy protective effect of the farming environment is also driven by the microbiome.

In the urban setting, what we breathe, eat, drink, touch, and how we exercise have changed. The gut, skin and mucosal microbiome is at stake, and so is inhaling enough biogenic chemicals, which have anti-inflammatory and anxiety-relieving effects. Biodiversity loss in the living environment may also endanger mental and sociocultural connections.

BIOLOGICAL MACHINERY FOR ADAPTATION AND RESILIENCE

The environmental exposure, the *exposome*, keeps alert the genetic (hardware) and epigenetic (software) machinery to regulate immunity for resilience. The learning is strongest during the first years of life, but also the elderly need contacts to wider nature.

***Question to the reader**. In future, does the advanced digital information with artificial intelligence learn to mimic the biological information network, the genetic and epigenetic machinery?*

A wide range of *non-communicable diseases* (NCDs) share microbial

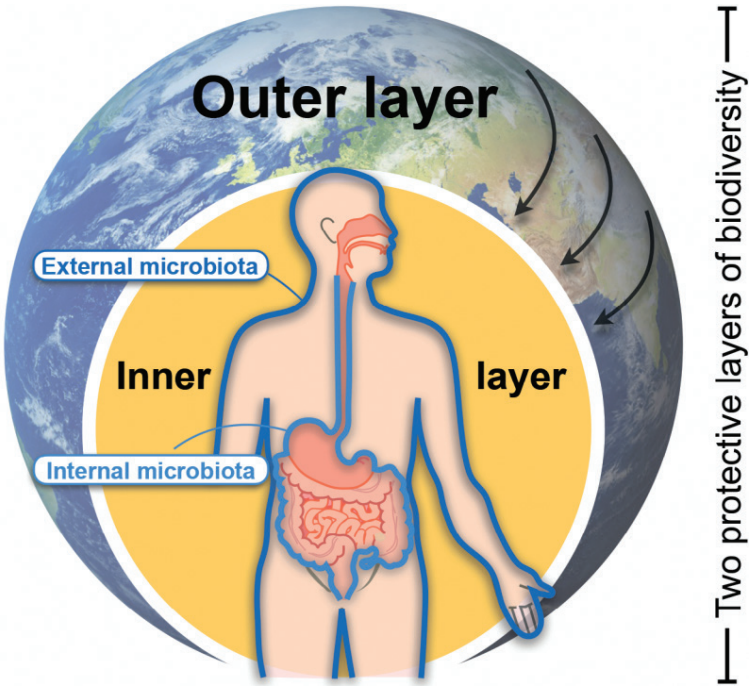

Figure 1 Humans are protected by two nested layers of biodiversity, consisting of bacteria and other micro-organisms residing in our bodies, both on the external and internal surfaces. The diversity and composition of the *inner layer* is dependent on microbial colonisation from the *outer layer*; a process that is under the influence of environment, behaviour, and lifestyle. *(Reprinted from Ruokolainen L, Lehtimaki J, Karkman A, Haahtela T, von Hertzen L, Laatikainen T. Holistic view of health: two protective layers of biodiversity. Ann Zool Fennici 2017;54:39-49)*

Figure 2 Urban, built environment (left), and changes in lifestyle have increasingly disconnected children from natural air, soil, and waters (right), the evolutionary home of *Homo sapiens*. The lower panels of butterflies illustrate biodiversity denoting a lot of species but in small numbers. High biodiversity ensures ecosystem stability and resilience. *(Photographs: Maria Andersson and TH Reprinted from Haahtela T. Biodiversity for resilience - What is needed for allergic children. Pediatr Allergy Immunol 2022;33:e13779)*

dysbiosis, immune imbalance, and low-grade inflammation (Figure 3). To cut the inflammatory circuits, immunotherapy and biologicals are used to treat many NCDs, even cancer. For allergy, immunotherapy was described already 113 years ago and is increasingly favoured.

NATURE DEFICIENCY

Nature deficiency refers to nature loss in the human body influencing health. Diagnosis, prevention, and treatment of the condition become part of the clinical practice, but validated *biomarkers* and evidence from interventions are needed. *Nature prescription* is likely to find plausible forms in patient care and inspire disease preventive actions at the society level. To restore gut microbiota, probiotics, and fecal microbiota transplantation are already practiced.

Allergies are environmental-driven diseases. Biodiversity hypothesis of allergy, and health in general, gives incentives for societies to integrate public health interventions and environmental care for sustainable future (Figure 4).

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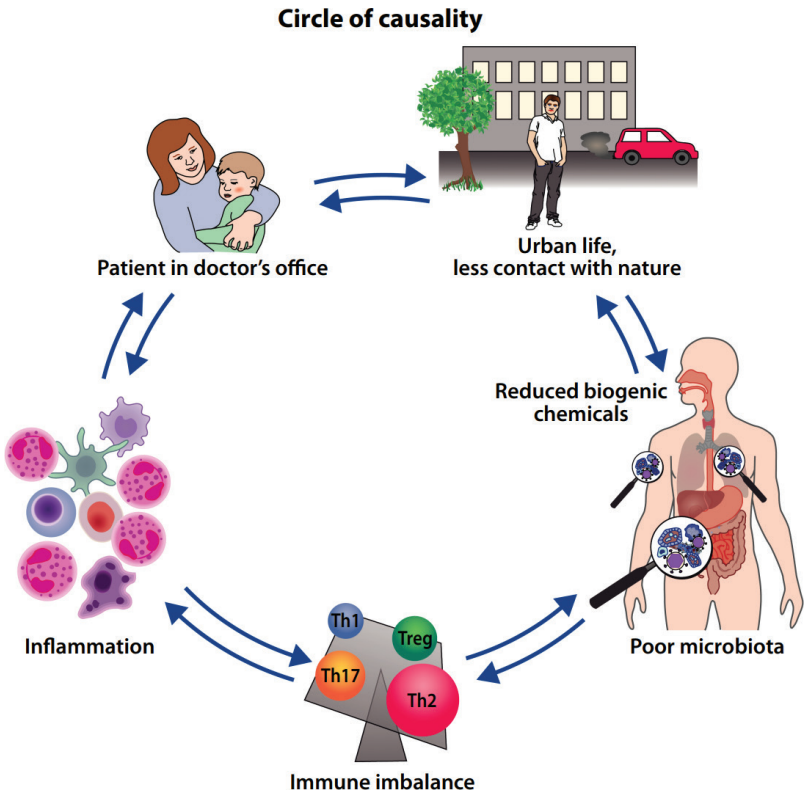

Figure 3 Urban living increases the risk of non-communicable diseases, allergy among them. In the doctor´s office, the circle can be cut, if *nature deficiency* is diagnosed and treated. For that, research on *biomarkers* and *current care guidelines* is called for. *(Reprinted from Haahtela T. Biodiversity for resilience - What is needed for allergic children. Pediatr Allergy Immunol 2022;33:e13779)*

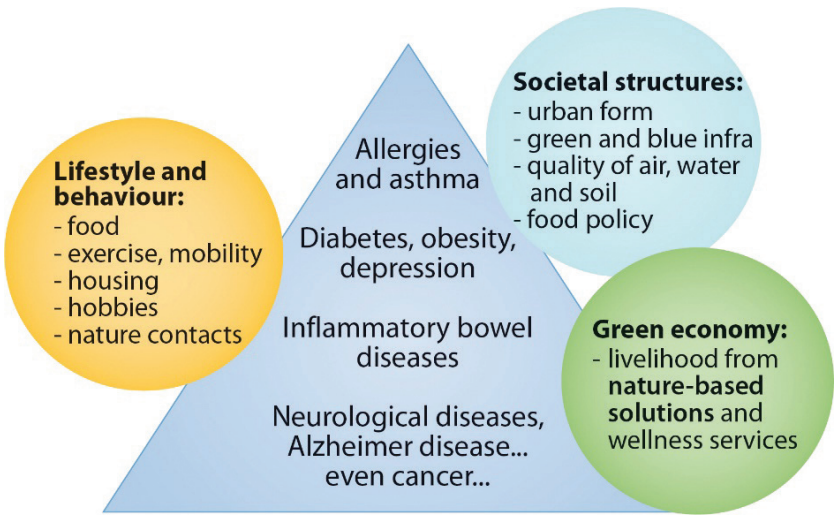

Figure 4 *Nature deficiency* can be, in part, compensated by taking natural elements back to the urban type of living. The whole society is needed to strengthen protective factors for health and mitigate risks. *(Reprinted from Haahtela T, Bousquet J, Anto JM. From biodiversity to nature deficiency in human health and disease. Porto Biomed J 2024;9:245)*

8 RESPIRATORY VIRAL INFECTIONS

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KEY MESSAGES

- Respiratory viral infections (RVIs) significantly contribute to global morbidity and mortality, and worsen chronic conditions like asthma and wheezing
- Planetary health challenges, including climate change, pollution, and biodiversity loss, are significant factors influencing the transmission and severity of RVIs, thereby intensifying their impact on asthma and allergies
- RVIs in the context of planetary health and asthma require a comprehensive approach that includes reducing climate change factors and improving control over the spread of RVIs

Respiratory viral infections (RVIs) represent a major global health challenge due to their considerable impact on morbidity and mortality, with millions of deaths worldwide each year from influenza, respiratory syncytial virus (RSV), and COVID-19. RVIs significantly contribute to chronic respiratory conditions such as chronic obstructive pulmonary disease (COPD), wheezing and asthma, and have been associated with the development of autoimmune disorders. Indeed, early-life RVIs can disrupt normal airway function and promote allergic sensitization, paving the way for long-term respiratory diseases.

RVIs are significantly affected by planetary health factors such as climate change, pollution and biodiversity loss, which further amplifies their impact on asthma and other chronic inflammatory disorders (Figure 1). First, the loss of biodiversity can lead to altered innate and adaptive immune system training, and therefore biased immune responses against RVIs and allergens. Second, RVIs are climate-sensitive diseases; thus, in recent years, the incidence peaks of some RVIs have shifted to warmer seasons. Climate change also heightens the risk of RVIs emergence and transmission by affecting viral biology, host susceptibility, human behavior, and environmental conditions. Low temperatures, humidity, and solar radiation are associated with seasonal peaks of influenza and RSV in temperate zones, while in tropical regions, increased rainfall is associated with higher transmission rates.

Pollen production and potency are exacerbated by climate change, imposing an additional strain on the respiratory system. Pollen also amplifies the risk of infectious diseases outbreaks and alters their epidemiology, may boost virus release, and it reduces antiviral gene expression and the release of several chemokines *in vitro*.

Climate change is associated with extreme weather events, including frequent heavy rainfall and thunderstorms. This can alter pollen degradation and enhance their long-distance transport. Airborne pollen grains can carry viruses, potentially amplifying their impact on public health. As a result, planetary health may influence the incidence of RVIs, by affecting allergen levels and triggering asthma outbreaks, a phenomenon known as thunderstorm asthma.

Finally, air pollutants can disrupt immune responses, increasing the vulnerability to respiratory infections and facilitating respiratory virus transmission. Population-based epidemiological studies offer strong evidence sug-

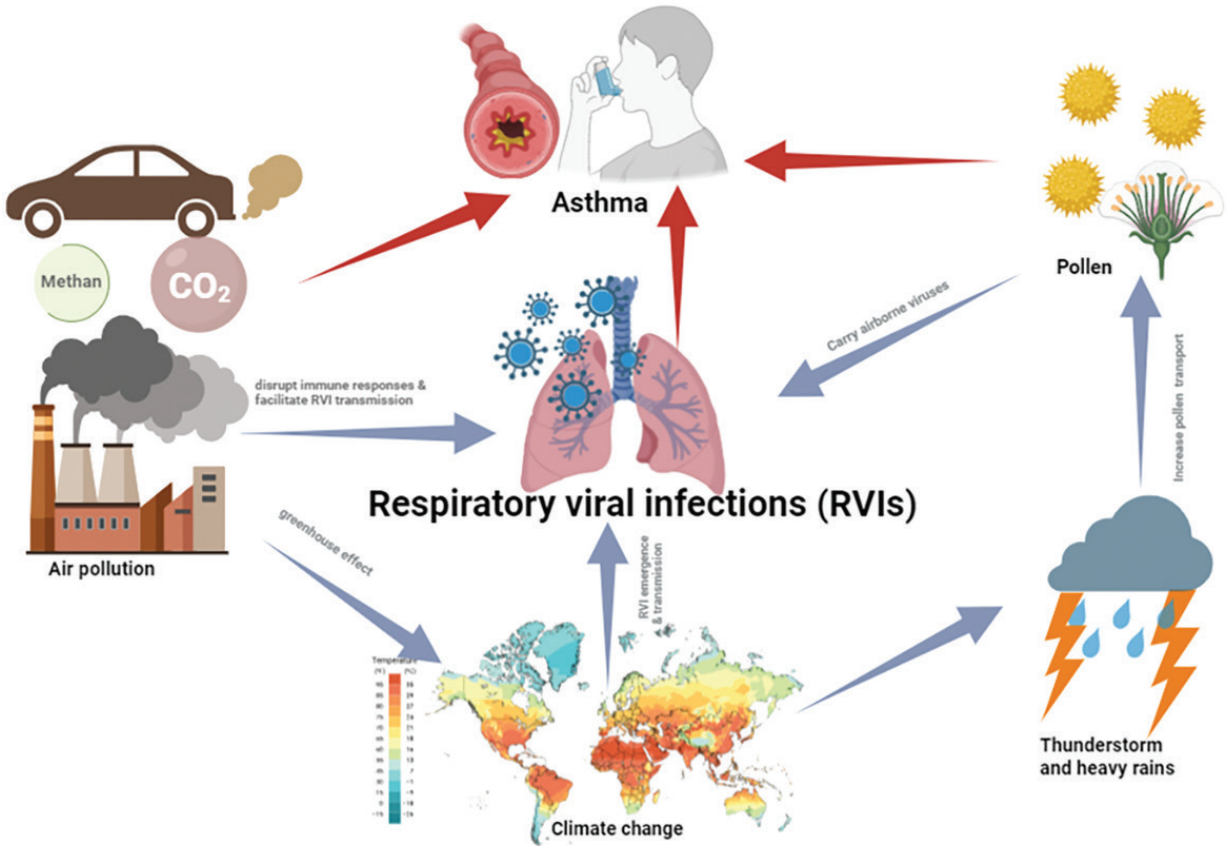

Figure 1 The interaction between planetary health, respiratory viral infections, and asthma. Red colored arrows indicate worsening of asthma clinical presentations.

gesting that short-term exposure to ambient air pollution, caused by burning of fossil fuels, may be linked to an increased incidence of influenza episodes. Additionally, pollution-driven indoor crowding further amplifies exposure to pathogens, creating a cycle of increased transmission.

Addressing the growing challenge of RVIs in the context of planetary health and asthma, requires a multi-faceted approach. This includes mitigating factors contributing to climate change, while in parallel reinforcing strategies to combat RVI spread such as vaccination programs, air quality improvements, and enhanced surveillance systems.

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9 MOLECULAR MECHANISMS OF EPITHELIAL BARRIER DEFECT

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KEY MESSAGES

- Genetic defects or harmful environmental exposures can disrupt epithelial integrity, leading to a cascade of immune activation and impaired barrier repair, increasing disease susceptibility
- Innate and adaptive immune responses, particularly cytokines such as IFN-γ, TNF-α, IL-4, and IL-13, as well as alarmins like IL-25, IL-33, and TSLP, contribute to type 2 inflammation over Th2 and ILC2 cells and to epithelial barrier dysfunction, facilitating pathogen colonization and microbial dysbiosis
- Key intracellular mechanisms contributing to epithelial barrier disruption include various forms of cell death, oxidative stress, endoplasmic reticulum (ER) stress, and unfolded protein response (UPR)
- Combined with genetic and epigenetic modifications, chronic inflammation hinders epithelial barrier repair, resulting in persistent permeability, microbial dysbiosis, and chronic inflammation

The epithelial barrier is a tightly packed layer of cells that protects underlying tissues and regulates the exchange of substances. Tight junctions (TJs), composed of protein complexes, are crucial for maintaining the integrity of this barrier against environmental challenges. Two primary pathways facilitate molecular transport across the epithelial barrier: transcellular and paracellular pathways. These junctions regulate the flow of immune cells, macromolecules, and ions, preserving cellular polarity and electrical resistance. The epithelial layer employs both transcellular and paracellular pathways for molecular transport. TJs operate through two primary routes: the pore and leak pathways. The pore pathway, mediated by claudin proteins, permits the selective passage of small ions and solutes through specific claudin channels. The leak pathway, regulated by proteins such as occludin, tricellulin, and zonula occludens (ZO) proteins at both bicellular and tricellular TJs, allows the selective passage of larger molecules.

Genetic defects or exposure to noxious agents can compromise the epithelial barrier, leading to epithelitis characterized by the release of alarmins and a temporary disruption of tight junctions. This disruption triggers an immune response, activating immune cells and promoting inflammation, further impacting barrier integrity, permitting unrestricted molecular passage, weakening the barrier, and increasing disease susceptibility. Studies have highlighted the influence of epigenetic modifications on epithelial integrity, building on the previously discussed genetic defects. Key roles have been identified for silent information regulator proteins, histone deacetylases, and CpG methylation in regulating tight junction stability in asthma. Inhibition of histone deacetylases has been shown to enhance barrier integrity by promoting the synthesis of tight junction proteins. Additionally, mutations in key epithelial proteins are implicated in allergic disorders. Polymorphisms in cytokine genes (e.g., IL-4, IL-13), alarmins (e.g., IL-25, IL-33, TSLP), inflammation-related proteins (e.g., ADAM33, HLA), and the vitamin D receptor are known to modulate asthma risk and severity. Genes

TABLE 1

Genes related to epithelial barrier fragility and predisposition to related diseases

Genes	Function	Associated Diseases
related to the structure of the epithelial barrier		
FLG (Filaggrin)	Aggregates keratin intermediate filaments and promotes disulfide-bond formation among the intermediate filaments during terminal differentiation of the epidermis.	Atopic dermatitis
ADAM33	A disintegrin and metalloproteinase domain-containing protein 33; influences airway remodeling	Asthma
MUC5AC	Involved in mucus production	Asthma, COPD
related to immune response and inflammation		
HLA	Human Leukocyte Antigen; presents peptides to immune cells	Various autoimmune diseases
IL4	Regulates immune response, involved in allergic responses	Asthma, allergic responses
IL13	Similar to IL4, it is critical in allergic inflammation	Asthma
IL33	Acts as an alarmin to signal immune cells	Asthma
TSLP	Promotes Th2 immune responses	Asthma, allergic diseases
IL1RL1	Acts similarly to IL33 in signaling immune responses	Asthma
CCL20	Recruits immune cells to inflammation sites	Inflammatory diseases
IL6	Proinflammatory cytokine, involved in immune responses	Various inflammation-mediated diseases
IRF4	Regulates gene expression in the immune system	Immune response, autoimmune diseases
TBX21	Regulates Th1 lineage development	Asthma, autoimmune diseases
FADS2	Involved in the biosynthesis of polyunsaturated fatty acids	Inflammatory responses
RUNX1	Regulates immune cell development	Blood diseases, immune responses

such as CCL20, IL6, IRF4, MUC5AC, TBX21, FADS2, and RUNX1 have also been associated with asthma. Moreover, next-generation sequencing has identified two single-nucleotide polymorphisms (SNPs) in the filaggrin gene linked to asthma pathogenesis (Table 1).

At the cellular level, multiple pathways are critical for maintaining or disrupting epithelial barrier integrity (Figure 1). NF-κB activation in epithelial cells leads to altered gene expression that promotes inflammation and cell death, ultimately impairing the barrier function. Oxidative stress also plays a pivotal role; the production of reactive oxygen species (ROS) damages proteins, lipids, and DNA, resulting in cellular dysfunction and death. Cellular processes such as phagocytosis and autophagy are involved in degrading and recycling macromolecules, contributing to epithelial homeostasis. Impaired autophagy is associated with increased susceptibility to barrier dysfunction due to the accumulation of damaged proteins and organelles. Additionally, endoplasmic reticulum (ER) stress and the unfolded protein response (UPR) are crucial in maintaining cellular homeostasis; when dysregulated, they lead to apoptosis and further epithelial barrier dysfunction. Surfactants also directly affect epithelial cells by modulating cell signaling pathways, reducing surface tension, and influencing immune responses, which can either stabilize or disrupt barrier integrity.

Interactions between the immune system and tight junction proteins are vital to maintaining barrier integrity. Epithelial cells, in response to stressors, release proinflammatory alarmins like TSLP, IL-33, and IL-25, which activate various immune cell types, including dendritic cells, macrophages, T-helper cells, and type 2 innate lymphoid cells (ILC2), initiating a Th2 immune response. In asthma and related conditions, released cytokines such as IL-4 and IL-13 further compromise barrier function by recruiting inflammatory cells, increasing mucus production, and enhancing IgE synthesis. Additionally, exposure to allergens or irritants can trigger IL-33 release, further disrupting tight junction integrity.

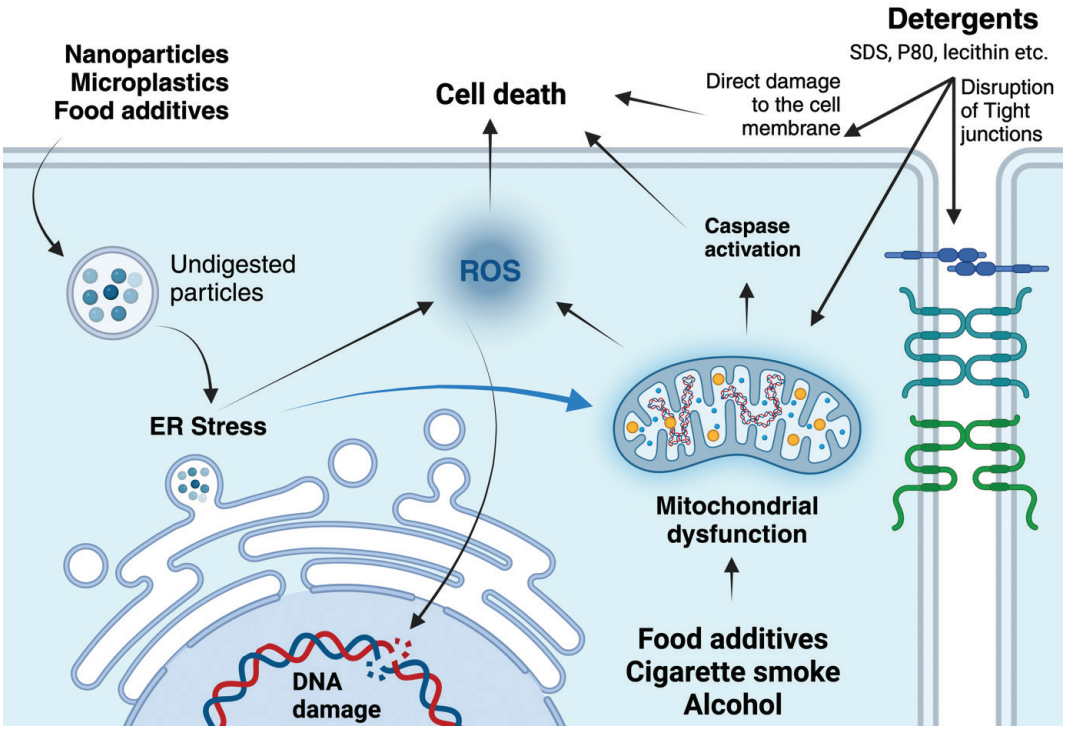

Figure 1 Mechanisms of Epithelial Barrier Disruption Induced by Cellular Stress. Various intracellular stress-induced mechanisms lead to epithelial barrier disruption. Endoplasmic reticulum (ER) stress is induced by undigested particles, contributing to cellular dysfunction. Reactive oxygen species (ROS) production results in oxidative damage to cellular components, while mitochondrial dysfunction, exacerbated by external factors such as food additives, cigarette smoke, and alcohol, further impairs epithelial integrity. Mitochondrial dysfunction also activates caspases, promoting cell apoptosis. DNA damage resulting from these stressors further compromises the epithelial barrier, leading to chronic dysfunction.

Chronic inflammation driven by commensals and pathogens in the gastrointestinal and respiratory tracts can contribute to persistent diseases in these tissues (Figure 2). The migration of activated immune cells to distal organs exacerbates inflammation systemically. Chronic stress also profoundly affects epithelial function by altering immune responses and barrier integrity. Stress-induced immune activation drives inflammation and barrier dysfunction, allowing increased infiltration of allergens and pathogens. Failure to restore barrier function due to persistent inflammation and epigenetic modifications perpetuates a cycle of barrier leakiness, microbial dysbiosis, and chronic inflammation, emphasizing the role of complex epigenetic regulation in maintaining barrier homeostasis. This cycle also involves processes such as 'washing away' inflammatory cells and cytokines through barrier openings and 'suppression' mediated by regulatory cytokines released by T cells and other cells on barrier surfaces, as seen during type 2 inflammation and exposure to high allergen doses in healthy individuals. The inability to restore epithelial barrier function due to sustained inflammation and epigenetic modifications results in persistent barrier leakiness, microbial dysbiosis, and chronic inflammation, highlighting the intricate relationship between epigenetic regulation and barrier integrity.

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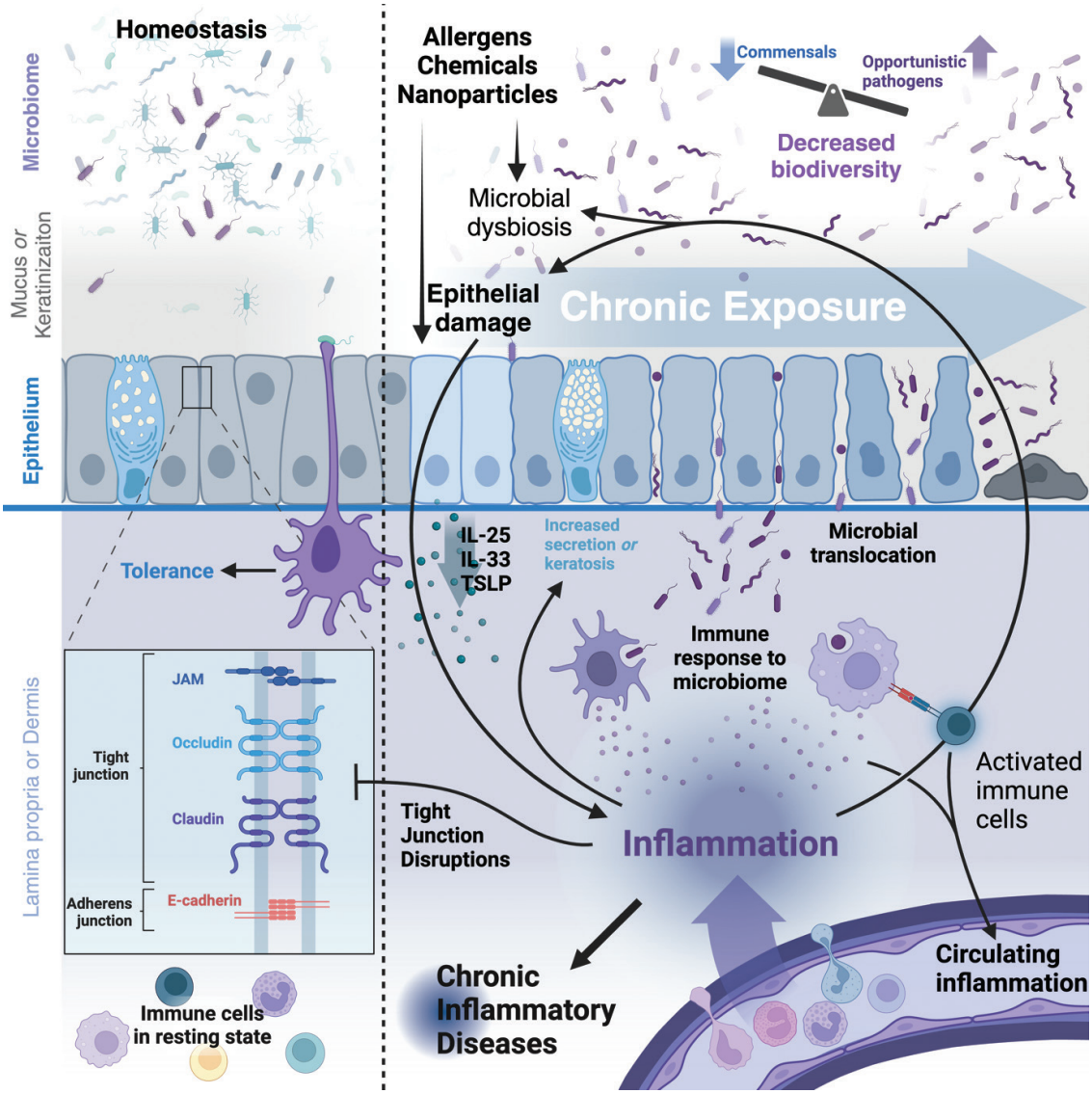

Figure 2 Impact of Chronic Exposure on Epithelial Barrier Integrity and Inflammatory Response. Chronic exposure to allergens, chemicals, and pollutants results in epithelial barrier damage, microbial dysbiosis, and reduced microbial diversity. Barrier disruptions lead to the release of alarmins, such as IL-25, IL-33, and TSLP, which induce type 2 inflammation, characterized by immune cell activation and increased keratosis or secretion. Tight junction disruptions facilitate microbial translocation, driving an immune response against the altered microbiome and contributing to chronic inflammation. Key junctional proteins, including JAM, occludin, claudin, and E-cadherin, are involved in maintaining epithelial barrier stability, while the disruption of these components contributes to chronic inflammatory diseases and circulating inflammation. JAM: Junctional adhesion protein; TSLP: Thymic stromal lymphopoietin.

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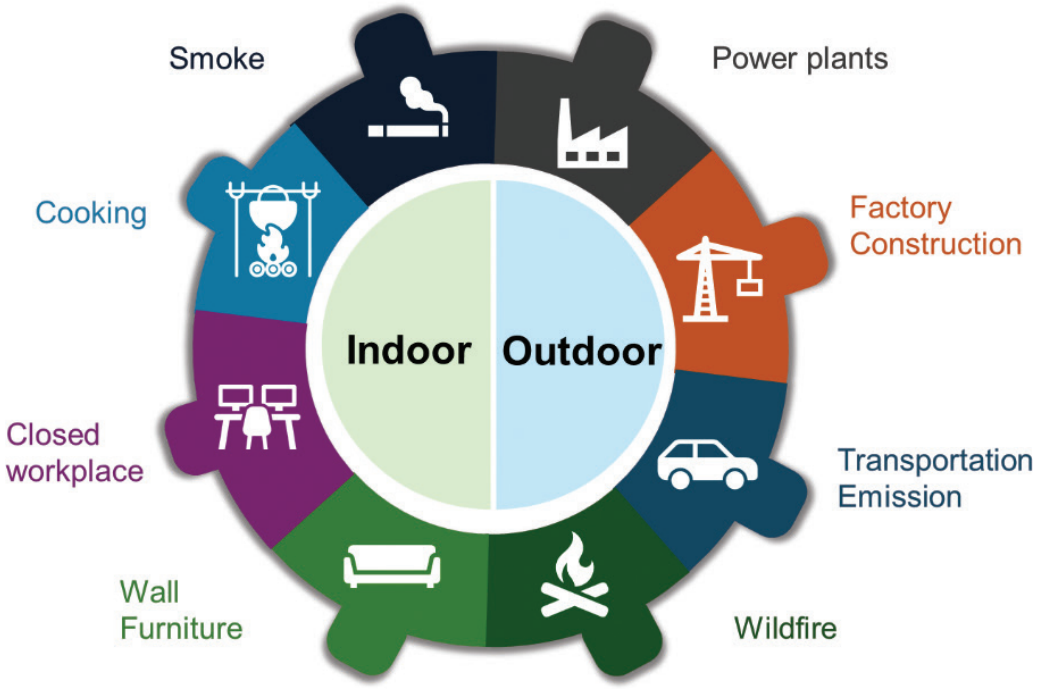
Section B

Indoor-outdoor air pollution



CHEMICAL POLLUTION

* Chemical air pollution
* Nitrogen oxides
* Ozone-induced lung disease
* Volatile organic compounds
* Sulphur oxides
* Endocrine disruptors
* Epithelial barriers and air pollution
* CO_2 exposure and diseases
* Epithelial barrier theory and laundry detergents
* Epithelial inflammation, cell death and barrier damaging effects of professional dishwashing
* Non-nutritive sweeteners and epithelial barriers
* Epithelial barriers and processed food additives

1 CHEMICAL AIR POLLUTION

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KEY MESSAGES

- Air pollution is now the greatest environmental risk factor to human health
- Chronic exposure to primary and secondary fine particulates ($PM_{2.5}$) is the largest driver of air pollution's burden of disease
- Indoor air pollution is an increasingly recognised threat to health, but far less is known about these emissions than those encountered outdoors
- Based upon improved epidemiology and toxicology, no safe levels of the common air pollutants have been identified. This has enabled the World Health Organisation to drastically lower their Air Quality Guideline/Limit values for $PM_{2.5}$ and NO_2
- As interim targets, the EU Council and Parliament agreed to reduce annual limit values by 2030 for $PM_{2.5}$ and NO_2 to 10 µg/m^3 and 20 µg/m^3 respectively

Domestic and industrial burning of coal for heat and energy has been responsible for horrendous air pollution such as the Great London Smog of 1952. Restricting coal burning was thought sufficient to deal with the problem, but clearly not the case. Air pollution is now the greatest environmental risk factor to human health accounting for 7 million (1 in 9) deaths worldwide. The principal outdoor pollutants are small particulates (PM_{10} and $PM_{2.5}$), nitrogen oxides (NOx, especially NO_2) and the photochemical pollutant, ozone linked to combustion. $PM_{2.5}$ is the largest driver of air pollution's burden of disease (Figure 1). Ambient pollutants continue to evolve with agricultural ammonia forming secondary inorganic aerosol with combustion emissions now accounting for 30% and 50% of $PM_{2.5}$ in the US and Europe respectively. Heavier electric vehicles produce more PM pollution from brakes and tyres and outdoor volatile organic chemicals are increasingly derived from personal and domestic sources. Apart from adverse health effects, the same pollutants from fossil fuel production and combustion are also short-lived climate pollutants. Indoor air pollution from combustion (especially biomass), household and personal products, building materials and furnishings is a growing concern (Figure 2).

While acute effects of air pollutants on lung and heart disease are widely recognized, it is the insidious long-term effects on health that is the major concern. Inhaled PM crosses the alveolar/capillary barrier to circulate and cause oxidant-induced low-level inflammation and damage in multiple organs, as well as being carcinogenic (Figure 3). Maternal PM crosses the placenta to blunt foetal organ development and increase premature birth and foetal death. Improved epidemiology and toxicology for all the common pollutants has shown that there are no safe health-related limits with those most severely affected being the disadvantaged. This evidence-driven insight has led to health-related annual limit values set by the WHO for PM_{10}, $PM_{2.5}$ and NO_2 being markedly reduced (Table 1).

Progress is being made in reducing emissions. Between 2005 and 2021, deaths in the EU attributable to $PM_{2.5}$ fell by 41%. However, further reducing outdoor air pollution in EU Member States to the 2021 WHO guideline values would further prevent annual deaths attrib-

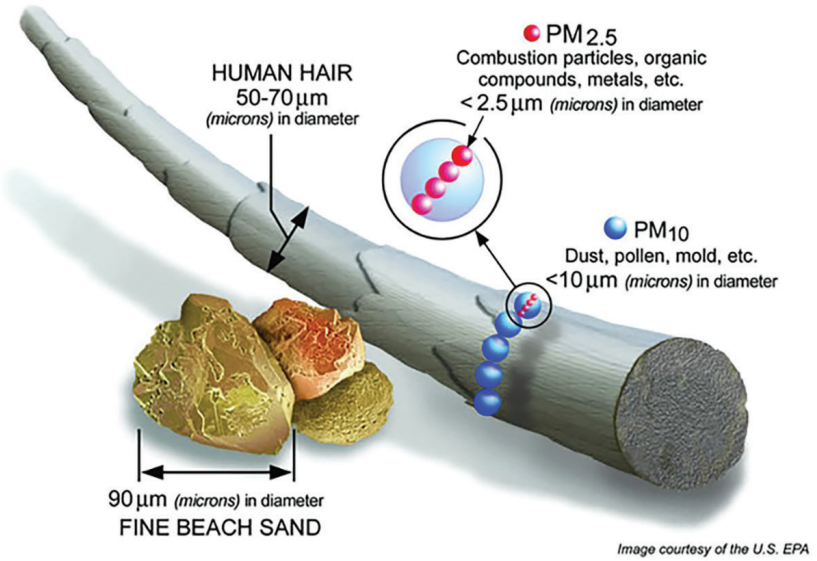

Figure 1 Size comparisons for particulate matter (PM) air pollution particles.

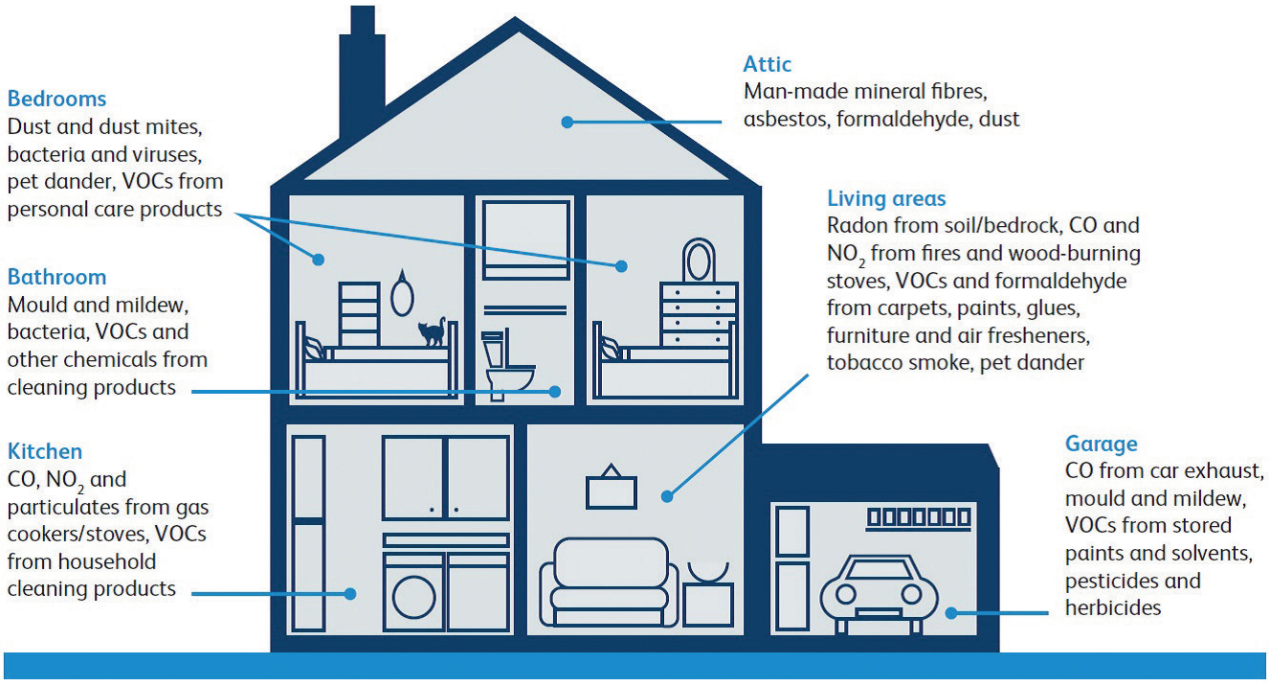

Figure 2 Sources and types of indoor pollution encountered in homes. VOCs = volatile organic compounds. Note that these lists are not exhaustive and that the actual pollutants present, and their amounts, will vary from household to household. *(Reprinted from Royal College of Physicians. Every breath we take: the lifelong impact of air pollution. Report of a working party. London: RCP, 2016)*

utable to $PM_{2.5}$, NO_2 and ozone by 253,000, 52,000 and 22,000 respectively. As interim targets, the EU Council and Parliament have agreed to reduce annual limit values by 2030 for $PM_{2.5}$ and NO_2 from 25 µg/m³ to 10 µg/m³ and 40 µg/m³ to 20 µg/m³ respectively.

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TABLE 1

Recommended WHO 2021 Air Quality Guideline (AQG) levels of principal outdoor air pollutants as compared to 2005 AQG values.

Pollutant	Averaging time	2005 AQGs	2021 AQGs
$PM_{2.5}$, µg/m³	Annual	10	5
	24-hour	25	15
PM_{10}, µg/m³	Annual	20	15
	24-hour	50	45
O_3, µg/m³	Peak season	-	60
	8-hour	100	100
NO_2, µg/m³	Annual	40	10
	24-hour	-	25
SO_2, µg/m³	24-hour	20	40

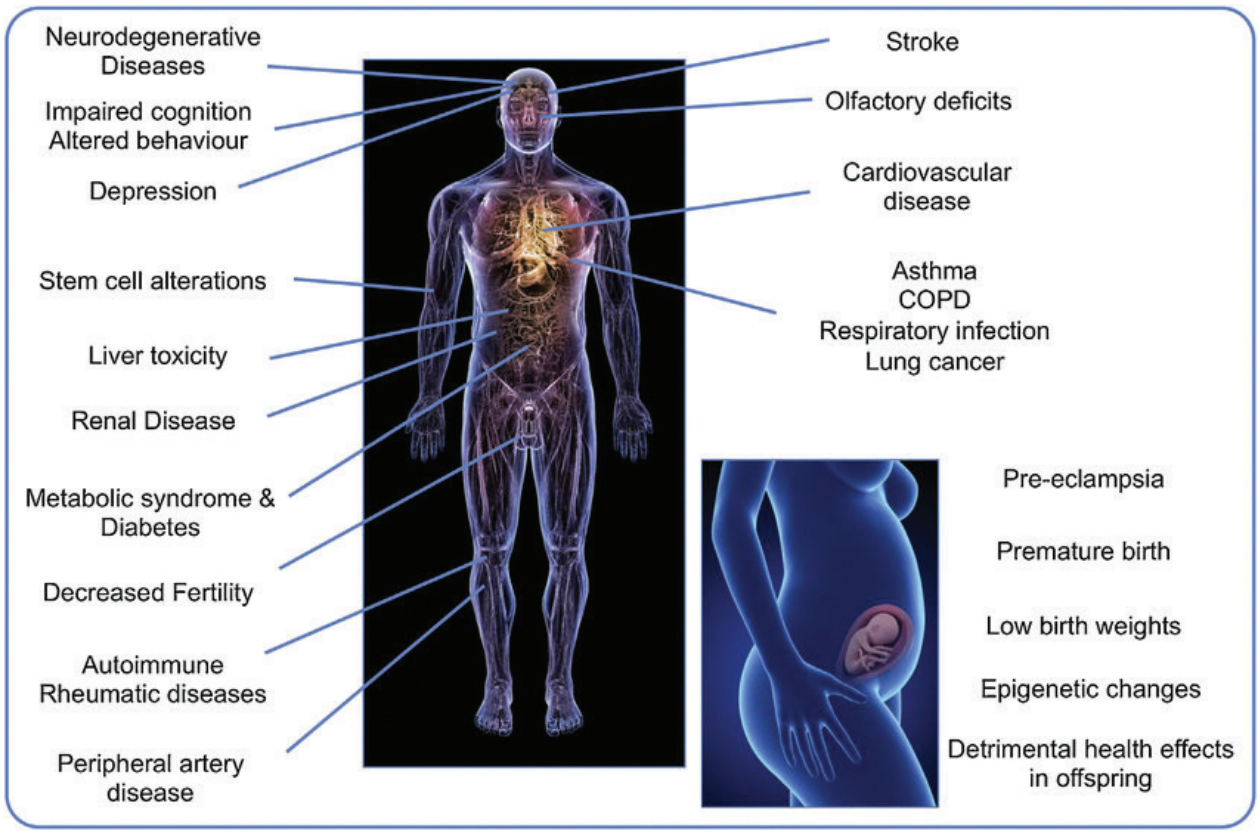

Figure 3 Multiple organs affected by air pollution contributing to disease and altered foetal development. *(Reprinted from Raftis JB, Miller MR. Nanoparticle translocation and multi-organ toxicity: A particularly small problem. Nano Today 2019;26:8-12)*

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2 NITROGEN OXIDES

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KEY MESSAGES

- Both short-term and long-term nitrogen oxides exposure has a detrimental impact on health
- Health impacts from nitrogen oxides exposure includes increased mortality, respiratory, cardiovascular and allergy-related outcomes
- From prenatal exposure to indoor exposure in the classroom, children continue to be at increased risk for the development of both asthma and increased emergency room visits and hospital admissions for asthma exacerbations due to increased NO_2 levels

Nitrogen oxides are an important contributor to climate change, with the impact of NO_2 on global warming being 265 times more potent to the atmosphere than carbon dioxide pound per pound. The primary source of outdoor NO_2 is from the burning of fossil fuels, such as from vehicle exhaust and industry, whereas indoor sources include natural gas stoves, space heaters, water heaters and filtration coming from outdoors. The distance between buildings and traffic also is associated with indoor NO_2 levels. Notably, when the amount of traffic sharply decreases (e.g. a city hosting the Olympics) or when industry shuts down (e.g. during the pandemic), the level of nitrogen oxides that a population is exposed to quickly decreases.

Research has consistently shown that nitrogen oxides impact the respiratory system for both short- and long-term exposure (Figure 1). Most recently, short-term exposure to NO_2 in children during the cold season was associated with a 10.1% increased risk of hospital admission for asthma for each 10 µg/m^3 increase in NO_2 levels. A recent meta-analysis also found that acute NO_2 exposure is associated with increased emergency room visits and hospitalizations for asthma exacerbations. Moreover, a nationwide birth cohort in Denmark found that prenatal exposure to air pollution, including NO_2, results in increased asthma risk as a child. A study also involving several cities in the US that are known for increased asthma incidence found that pediatric hospital admissions for asthma exacerbations correlate with the cyclic and seasonal pattern of NO_2. For indoor air quality, classroom NO_2 levels of children with asthma is associated with increased airflow obstruction. Indoor NO_2 levels may also be associated with reduced lung function in those with more severe COPD. Finally, exposure to high NO_2 levels may increase the risk of lung cancer in patients with idiopathic pulmonary fibrosis.

More recently, air pollution research has also found that even long-term exposure to low levels of NO_2 is associated with all-cause mortality (hazard ratio of 1.17 (95% CI: 0.92-1.50 per 10 µg/m^3) and heart failure for both short-term (odds ratio 1.016 (1.005-1.026; I^2 = 53.7 %) and long-term (odds ratio 1.072, 1.028-1.118; I2 = 78.3%) increases of 10 µg/m^3 NO_2. And especially for genetically predisposed patients, long-term exposure to NOx and NO_2 (median follow-up period of 12.5 years) was associated with an increased risk of allergic rhinitis (NO_2 hazard

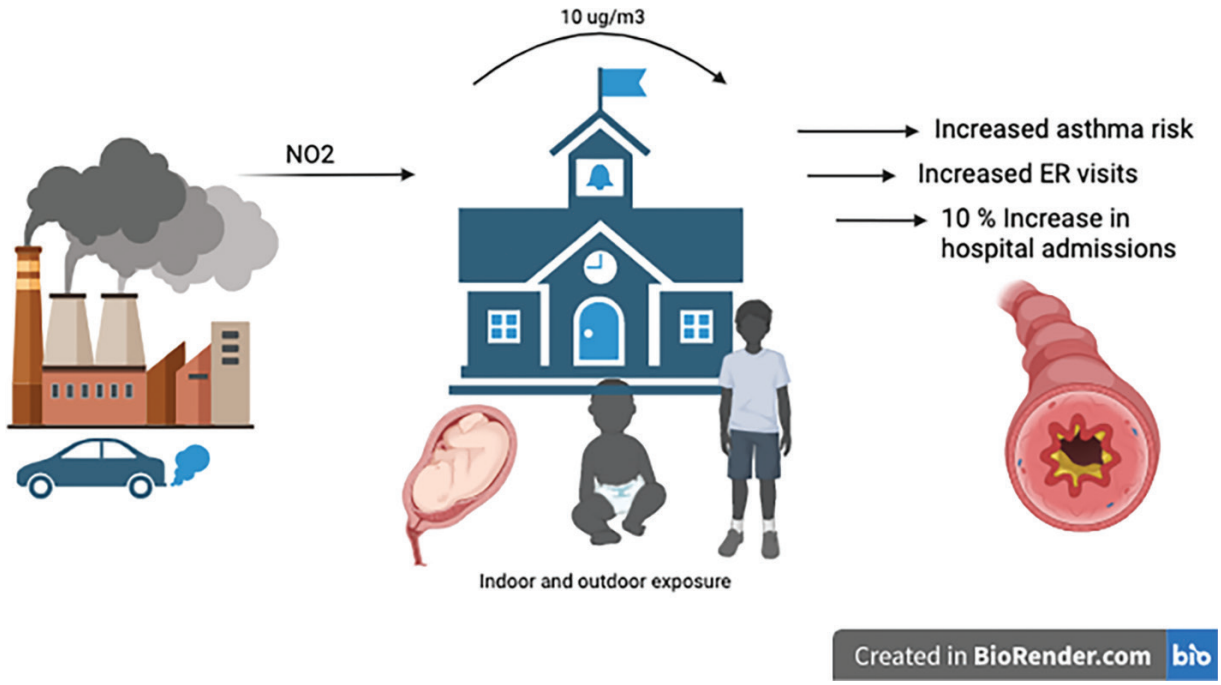

Figure 1 Impact of NO_2 on children.

ratio 1.14, 95% CI: 1.09-1.19, per 10 µg/m^3; NOx hazard ratio 1.10, 95% CI: 1.05-1.15, per 20 µg/m^3).

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3 OZONE-INDUCED LUNG DISEASE

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KEY MESSAGES

- Acute high dose ozone exposure triggers severe acute respiratory distress syndrome (ARDS)
- Chronic ozone exposure causes chronic obstructive pulmonary disease- (COPD) and asthma-like disease
- Ozone induces oxidative stress in many cells in the lungs leading to reactive oxygen species (ROS)-induced activation of Toll-like receptors (TLRs), NOD-like receptors (NLRs) and inflammasomes, causing cellular damage with the release of interleukin-1β (IL-1β), and many other proinflammatory mediators, including lipid mediators chemokines and cytokines.
- Ozone exacerbates chronic lung diseases
- Therapeutic targets are emerging

OZONE-INDUCED RESPIRATORY EFFECTS

Early studies in human volunteers and mice predicted ozone-induced lung disease. Ozone induces oxidative cell injury triggering an inflammatory response. Prolonged exposure is associated with increased morbidity and mortality, along with heightened responses to microbial or allergen challenges. Acute exposure causes acute lung injury characterized by damage to the respiratory epithelial barrier, resulting in protein leakage and the release of inflammatory mediators and neutrophil recruitment. The respiratory mucosal barrier, consisting of various epithelial cell subsets, dendritic cells, macrophages, resident adaptive immune cells, endothelial cells, fibroblasts and smooth muscle cells, is the initial structure exposed to ozone, undergoing cell stress and death of alveolar, bronchiolar epithelial and other cells with protein leakage into bronchoalveolar lavage fluid (BALF) and the release of mediators such as IL-1α and IL-1β, IL-25, IL-33, TSLP, leukotrienes, prostaglandins, and chemokines (Figure 1A).

Chronic exposure to ozone (twice weekly at 1.5 ppm for 90min) in mice, induces chronic inflammation, with destruction of alveolar epithelial cells and the development of emphysema within six weeks (Figure 1B). This pattern closely resembles that found in patients with chronic obstructive pulmonary disease (COPD).

INNATE AND ADAPTIVE IMMUNE RESPONSE INDUCED BY OZONE EXPOSURE

An immediate immune response, part of innate immunity, is initiated by endogenous or environmental danger or injury events. NLRP3 and other inflammasomes are activated forming a multimeric complex, consisting of the adaptor protein ASC and caspase-1. This complex plays a pivotal role in processing and secretion of the proinflammatory mature form of IL-1β, contributing to the inflammatory response. Upon activation, caspase-1 cleaves inactive pro-IL-1β precursor proteins, into their active IL-1β/ IL-18 fueling inflammation via activation of IL1RI and IL-18R on the surface of many cells. IL-1β and IL-1α trigger acute respiratory barrier injury, inflammation and airway hyperreactivity dependent on IL-1R1 and on the adaptor protein myeloid differentiation factor-88 (MyD88). Epithelial cell signaling is critical, since deletion of MyD88 in lung type I alveolar epithelial cells reduces ozone-induced

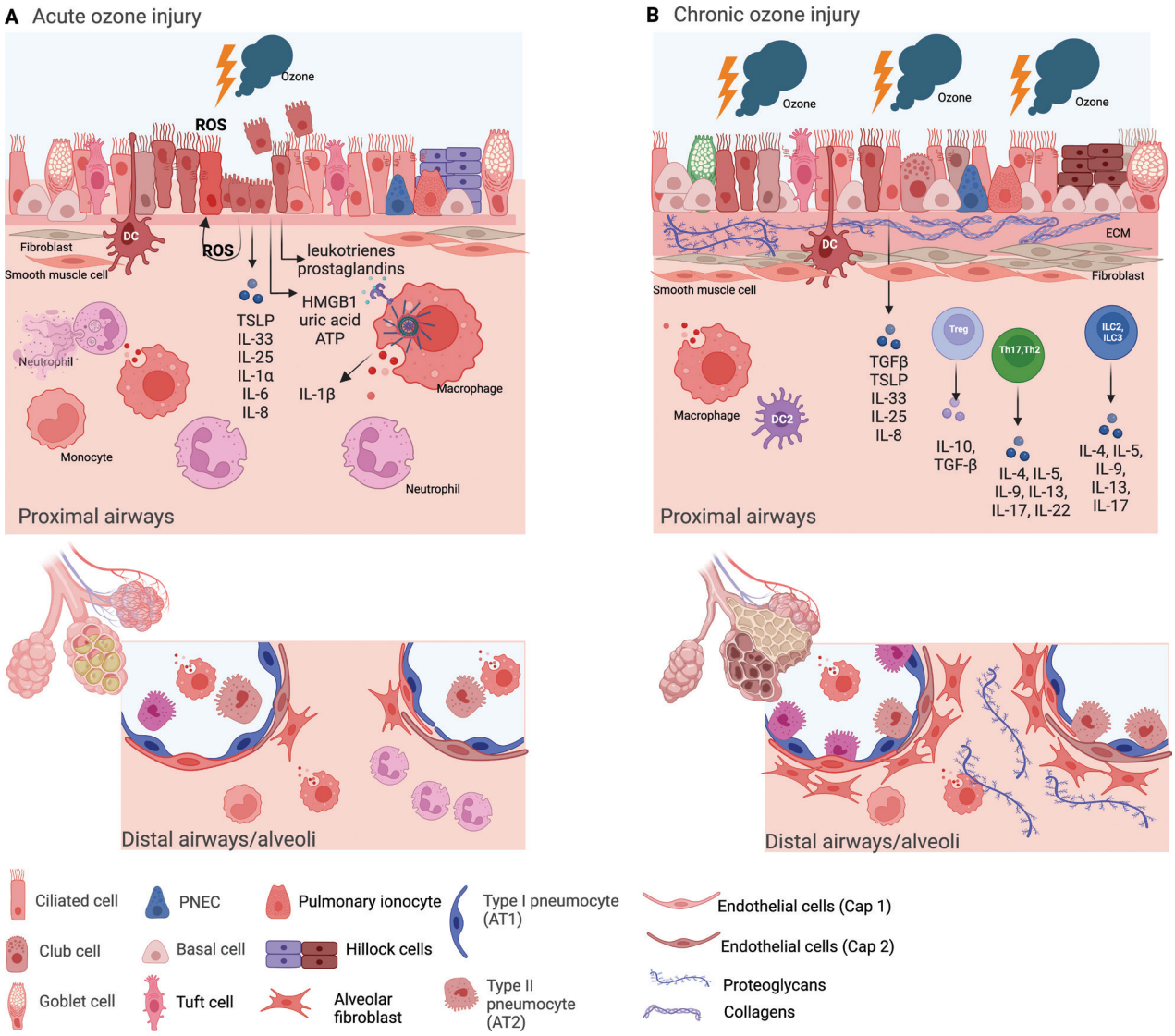

Figure 1 Effects of acute and chronic exposure to ozone in the lungs. A. Acute exposure to high doses of ozone leads to the acute lung injury affecting proximal (upper panel) and distal (lower panel) airways. There is an oxidative stress-induced production of reactive oxygen species (ROS) in epithelial cells and other structural and immune cells of mucosal barriers. Cell stress and ROS lead to the damage of tight junction complexes between epithelial cells, protein leak, and the release of a wide variety of further danger signals including mtDNA, ATP, uric acid, HMGB1, many of which further activate TLRs and NLRs in interstitial and alveolar macrophages (MΦ) and dendritic cells (DC). This leads to activation of NLRP3 inflammasome in these cells and release of active forms of IL-1β and IL-18. Activated and damaged epithelial cells release epithelial alarmins (i.e. IL-33, TSLP, IL-25, GM-CSF), other proinflammatory cytokines (IL-1α, IL-6), chemokines (eg. CXCL8, also known as IL-8) and lipid mediators, which leads to the biphasic acute inflammatory response, with infiltration and activation of neutrophils and macrophages. B) Chronic exposure to ozone, leading to repeated cycles of epithelial injury and repair result in proximal and distal airway remodeling (overproduction of extracellular matrix components, increased production of TGFβ), chronic type 17 and type 2 inflammation, a progressive destruction of alveolar epithelial cells and development of emphysema. Figure created with Biorender.com.

inflammation. IL-1β can be released from virus-infected epithelial cells upon activation of RIG-I inflammasome. **Interleukin 33 (IL-33)** exhibits a biphasic response following a single ozone exposure and plays a complex role in ozone-induced lung injury. A rapid disruption of the epithelial barrier within 1 hour is followed by a second phase of respiratory barrier injury characterized by increased neutrophil recruitment, reactive oxygen species production, airway hyperresponsiveness, and IL-33 expression. In the absence of IL-33 or the IL-33 receptor/ST2, epithelial cell injury and myeloid cell recruitment are augmented, but the expression of ROS in neutrophils and airway hyperresponsiveness are diminished. **Transforming growth factor β (TGF-β)** plays a critical role in the development of chemical-induced lung fibrosis. Ozone-induced emphysema and pulmonary fibrosis in mice may be mediated by TGF-β. Chronic ozone exposure increased levels of TGF-β protein in BALF and plasminogen activator inhibitor 1 (PAI-1), along with lung fibrosis. Blockade of the TGF-β signaling pathway suppresses ozone-induced Smad2/3 phosphorylation, PAI-1 and collagen expression, and α-smooth muscle actin (α-SMA) deposition in the lung. **Interleukin 17A (IL-17A)** also activates Th17 immune responses induced by acute and chronic ozone exposure. **Aryl hydrocarbon Receptor (AhR)** is activated upon chronic ozone exposure and associated with increased tryptophan and lipoxin A4 production in mice to prevent inflammation, airway hyperresponsiveness and tissue remodelling via reduction of IL-22 expression. Finally, several **epithelial chemokines** and **lipid mediators** act as signaling molecules, guiding immune cells to the site of inflammation and promoting their adhesion to endothelial cells exacerbating tissue damage, inflammation and fibrosis.

EXACERBATION OF CHRONIC AIRWAY DISEASES BY OZONE EXPOSURE

Epidemiological and experimental studies provide evidence supporting a correlation between air pollution and heightened incidence and severity of chronic airway diseases, including asthma and COPD. The adverse effects of ozone, nitrogen dioxide, and particulate matter (PM) are well-documented. Further, the allergen response in ozone-exposed mice is heightened by increased airway hyper-responsiveness, elevated recruitment of neutrophils and eosinophils in the BALF, and intensified lung inflammation marked by augmented goblet cells, myofibroblasts, and smooth muscle cells. It resembles the mechanisms of asthma exacerbations during the combined exposure of allergens and respiratory viruses in patients with asthma.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH INFLAMMATION, FIBROSIS AND EMPHYSEMA

COPD represents a significant public health concern investigated in studies involving cigarette smoke, particulate matter and ozone exposure. Ozone exposure in mice (1.5 ppm, twice weekly for 6 weeks) causes airway hyperresponsiveness with eosinophils and neutrophils, activation of Th2 and Th17 immune responses, emphysema, impaired repair, and fibrosis mirrors the characteristics observed in patients with COPD (Figure 1B). Cholinergic signaling contributes to this response and the muscarinic inhibitor tiotropium, widely used in COPD therapy inhibit airway hyperresponsiveness, IL-5 production, myeloperoxidase (MPO) activity, and eosinophil recruitment.

THERAPEUTIC TARGETS FOR PHARMACOLOGICAL INTERVENTIONS

The experimental data offer promising drug targets for mitigating ozone-induced chronic inflammatory lung disease. Nonetheless, the efficacy of therapeutic interventions tested in mouse models necessitates validation through clinical studies. Below, we outline the potential efficacy of agonists or antagonists that merit consideration for inclusion in clinical trials (Table 1). Further understanding the pathways underlying chronic inflammatory lung diseases may uncover additional targets. However, reducing airborne air pollution is the most efficient way to reduce chronic lung disease.

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TABLE 1

Potential therapeutic targets in ozone-induced lung injury

Potential targets	References
TNF neutralization	Williams et al. Am J Physiol Lung Cell Mol Physiol 2015
Blockade of IL-1β using available neutralizing antibodies (canakinumab) and the IL-1 receptor antagonist (Anakinra)	Michaudel et al. Am J Clin Exp Immunol 2016; Michaudel et al. Front Immunol 2018
Neutralizing antibodies targeting IL-22 and IL-17A	Mathews et al. PLoS One 2014; Michaudel et al. Front Immunol 2020
TLR4 antagonists	Peri and Piazza Biotechnol Adv 2012; Zhang et al. Eur J Med Chem 2022
Inhibition of NLRP3 inflammasome activation using specific inhibitors (MCC950)	Coll et al. Nat Med 2015; Haag et al. Nature 2018; Hooftman et al. Cell Metab 2020
Blockade of nucleic acid sensor activation, notably cGAS/STING, using antagonists	Haag et al. Nature 2018
Blockade of cholinergic pathways	Yamada and Ichinose Curr Opin Pharmacol 2018
Blockade of muscarinergic pathways (Tiotropium and related analogs)	Bateman et al. Pulm Pharmacol Ther 2009; Kerstjens et al. Respir Med 2016; Kistemaker et al. Br J Pharmacol 2019; Tashkin et al. Respir Med 2016; Wollin and Pieper Pulm Pharmacol Ther 2010
ROS inhibitors such as N-acetyl cysteine, and hydrogen disulfide	Wiegman et al. Front Immunol 2020
Microbial metabolites such as butyrate activate GPR109A/HCAR2, inhibiting inflammatory diseases.	Correa et al. Front Nutr 2022; Lewis et al. Front Immunol 2019; Losol et al. Clin Transl Allergy 2024
Histone modulators such as histone deacetylases (HDAC) may be another approach using HDAC inhibitors	Fellows and Varga-Weisz Mol Metab 2020
DNase treatment	Liu et al. Int Immunopharmacol 2023; Yadav et al. Int Immunopharmacol 2023
N23Ps (N-(2-methoxyphenyl)-3-(phenyl)acrylamides) are novel compounds suppressing myofibroblast transdifferentiation and collagen deposition	Gerckens et al. Sci Adv 2021

4 VOLATILE ORGANIC COMPOUNDS

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KEY MESSAGES

- VOCs are present in both indoor and outdoor environments
- VOCs persist for many hours after initial exposure and are absorbed by the body
- Exposure increases the risk of new-onset asthma and worsens signs and symptoms of ongoing asthma
- VOCs produced by the body may act as disease biomarkers

Low molecular weight carbon-based compounds that are gaseous at room temperature are known as volatile organic compounds (VOCs). These are released from many household products such as cleaning and disinfecting materials, cosmetics, furnishings, office equipment including photocopiers and printers, glues and marker pens as well as pesticides. In addition, VOCs are also generated in many industrial processes including the production of fuels, pharmaceuticals, paints, coolants as well as in wastewater processing. They are also found as contaminants in ground water in and around urban environments. Environmental VOCs are collected using stationary monitors and a variety of different devices and subsequently analysed using mass spectroscopy (GM-MS). The lack of personalised or sometimes even local monitoring of VOC levels and standardisation of collection has hindered the identification of temporal and concentration relationships between VOC exposure and asthma.

The US Environmental Protection Agency (EPA) recently reported that the levels of indoor VOCs are generally 2-5-fold greater than those seen outside irrespective of whether the accommodation is in a rural or urban area (https://www.epa.gov/indoor-air-quality-iaq/what-are-volatile-organic-compounds-vocs). In addition, high airborne levels of indoor VOCs such as cosmetics and disinfectants may persist for many hours after their initial use. This is important as VOCs can be inhaled or absorbed by the skin to affect cell and organ function and eventually impact on human disease. Interestingly, indoor formaldehyde levels are particularly high in new houses and formaldehyde exposure is associated with a significant increase in the risk of asthma in children, but not in adults. Furthermore, exposure to formaldehyde but not benzene, toluene and xylenes, may be associated with a higher risk of new-onset wheeze in atopic patients with no impact of these or of total VOC exposure on lung function.

Recent studies suggest that exposure to high levels of environmental, especially indoor, VOCs may increase the risk of new-onset asthma and asthma symptoms with a greater effect with indoor exposure to benzene, toluene, and p-dichlorobenzene for example. Several environmental factors are associated with adult-onset asthma including smoking, obesity and exposure to indoor VOCs such as formaldehyde. Other VOCs linked to a raised asthma risk include alcohols, aldehydes, alkanes, chlorinated hydrocarbons, propylene glycol and glycol ethers. In addition, acute high level VOC exposure may increase symptoms of asthma despite the mean exposure being below acceptable daily exposure levels. VOC exposure of individuals is greater in subjects living in deprived areas of Pittsburgh where the incidence of uncontrolled asthma and of se-

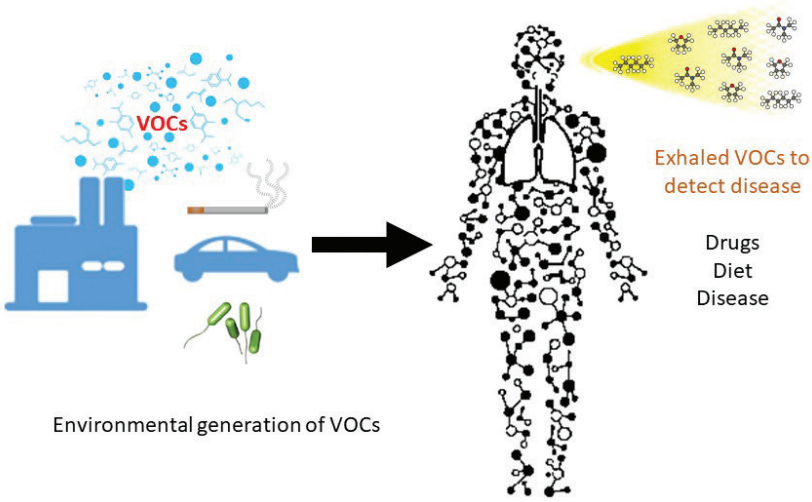

Figure 1

vere asthma was greatest. Animal models of asthma also indicate that VOCs can induce airway inflammation, excess mucus production and an enhanced T2 immune response.

Future research should focus on more personalized monitoring and treatment plans for mitigating exposure such as changing building materials and household products together with improved ventilation, dehumidification and air purification.

VOCs are not only generated in the external environment but are also made by metabolic processes in the body and analysis of these exhaled VOCs, also known as breathomics, have been used to distinguish health from asthma and or between different phenotypes of asthma. Compared to the measurement of environmental VOCs, exhaled VOCs are detected using 2 main sampling methods namely mass spectrometry (GC-MS) and chemical sensors or eNoses. The later provides patterns of exhaled VOCs without identifying the specific components whilst the former gives precise measurements of components and their levels.

Due to the ease of use of eNoses, detailed analysis of VOC profiles, particularly in children, may lead to better sub-phenotyping of asthma and identify children at risk for developing the disease. VOCs that are most often reported to discriminate between airways diseases are carbonyls such as aldehydes, esters and ketones and hydrocarbons including alkanes and alkenes. Furthermore, although exhaled ethane and 3,7-dimethylnonane have been reported as being a discriminatory biomarker for type 2 asthma these require confirmation in other cohorts. Indeed, there is little concordance across VOC studies due to a lack of standardisation and measures of stability.

It is also important to account for the impact of treatment, diet, co-morbidities such as the presence of metabolic syndrome and the contamination with environmental VOCs which can persist for many days. For example, there are significant associations between drug metabolites in the urine and exhaled VOCs. These variations will improve with the publication of technical standards and result in the generation of clinically meaningful thresholds for the identification of asthma and its subtypes between healthy subjects and patients with other diseases.

Cigarette smoking and the use of e-cigarettes has a profound effect on exhaled VOC profiles. Cigarette smoking is associated with raised levels of 2,5-dimethylfuran, benzene, toluene and xylenes whilst e-cigarette use with elevated benzaldehyde, toluene, methylheptane, trichloroethylene and d-Limonene. These, and other risk factors such as diet, must be taken into consideration in future biomarker research to prevent biomarkers of risk factors being attributed to disease.

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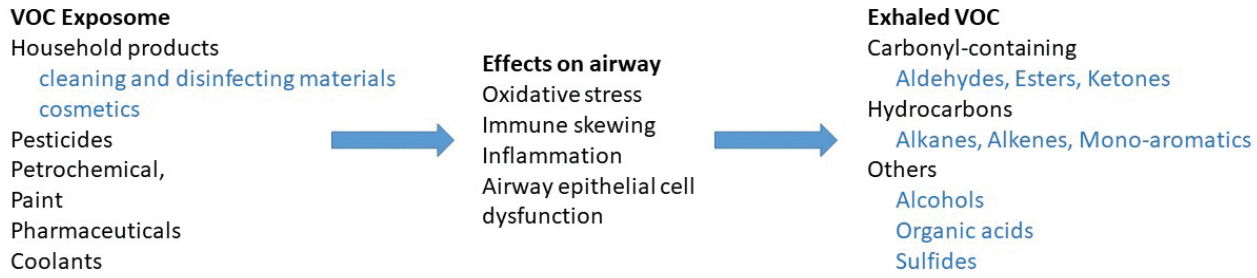

Figure 2

TABLE 1

Key questions for VOC analysis in asthma
Which environmental VOCs impact on asthma risk, incidence, severity and lung attacks?
Optimise VOC measurement and how to account for intrinsic- versus extrinsic-generated compounds.
Which intrinsic VOCs best define asthma vs health and asthma (sub)phenotypes e.g. T2
Identify intrinsic VOCs that indicate asthma incidence, lung function, severity and attacks.
What impact do specific drugs/therapy have on exhaled VOC profiles?
Identify the risk factors that interfere with exhaled breath VOC analysis.

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5 SULPHUR OXIDES

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KEY MESSAGES

- Sulphur dioxide (SO_2) is among the main outdoor air pollutants associated with increased respiratory health risk
- Major sulphur dioxide sources are fossil fuel combustion, roasting of sulphide minerals, vehicles and -to a lesser degree- natural sources
- Exposure at high concentrations of SO_2 are associated with augmented risk of respiratory mortality and asthma exacerbations
- Emission reduction of main five pollutants must be met; to date the most significant progress in decrease trends has been shown for SO_2 emission

According to the World Health Organization (WHO), air pollution is one of the major environmental health risks, particularly associated with increased risk of cardiovascular diseases, lung cancer and respiratory disease, including asthma. Sulphur dioxide (SO_2) is among the main outdoor air pollutants, along with carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), particulate matter (PM), and traffic-related air pollution (TRAP). Sulphur oxides are formed by fossil fuels (mainly coal or oil) combustion and by metal smelting and other industrial processes, so that major sources of SO_2 emissions are represented by power stations, metal extraction, vehicles, and natural sources like volcanoes.

Sulphur oxides are harmful gases emitted into the atmosphere, acting as an irritant on the mucous membranes of the upper and lower respiratory tract. High concentrations of SO_2 can impact respiratory health causing inflammation, cough and increasing the risk of respiratory infections.

A recent systematic review on sulphur dioxide and daily mortality estimated a meta-analytic effect for respiratory mortality of RR = 1.0067 (95% CI 1.0025-1.0109) per 10 µg/m³ sulfur dioxide, with a moderate certainty of the evidence according to GRADE.

Short-term exposure to SO_2 can damage the human respiratory system, especially in individuals with asthma and at-risk age groups, such as children and elderly. In a recent metanalysis short-term exposure to daily SO_2 has been associated with a moderate certainty of evidence with an increased risk of asthma exacerbation in terms of asthma-associated emergency room visits (ERVs) and hospital admissions (HAs), after 1 hour and 24 hours after exposure.

In more recent meta-analytical results, the association between increased exposure to SO_2 with increased risk of asthma exacerbation has been demonstrated with different quality of evidence based on the time passed since exposure. In particular, exposure to a 10 mcg/m³ increase of SO_2 above the WHO threshold is possibly associated with increases in asthma-related ERVs with low certainty of evidence at lag days 0 to 3, while the same exposure level is associated with moderate certainty evidence to increased risk for asthma-related HAs at lag 1.

Regulation policies and personal are necessary to reduce air pollutants below the WHO threshold.

TABLE 1

WHO global air quality guidelines recommendations on AQG levels with interim targets for sulphur dioxide (1).

Pollutant	Averaging time	Interim target				AQG level
		1	2	3	4	
SO_2, µg/m^3	24-hour *	125	50	-	-	40

** 99th percentile (i.e. 3-4 exceedance days per year)*

AQG levels: (lowest levels of exposure for which there is evidence of adverse health effects).

Interim targets: air pollutant levels which authorities in highly polluted areas can use to develop pollution reduction policies that are achievable within realistic time frames. Therefore, the interim targets should be regarded as steps towards the ultimate achievement of AQG levels in the future

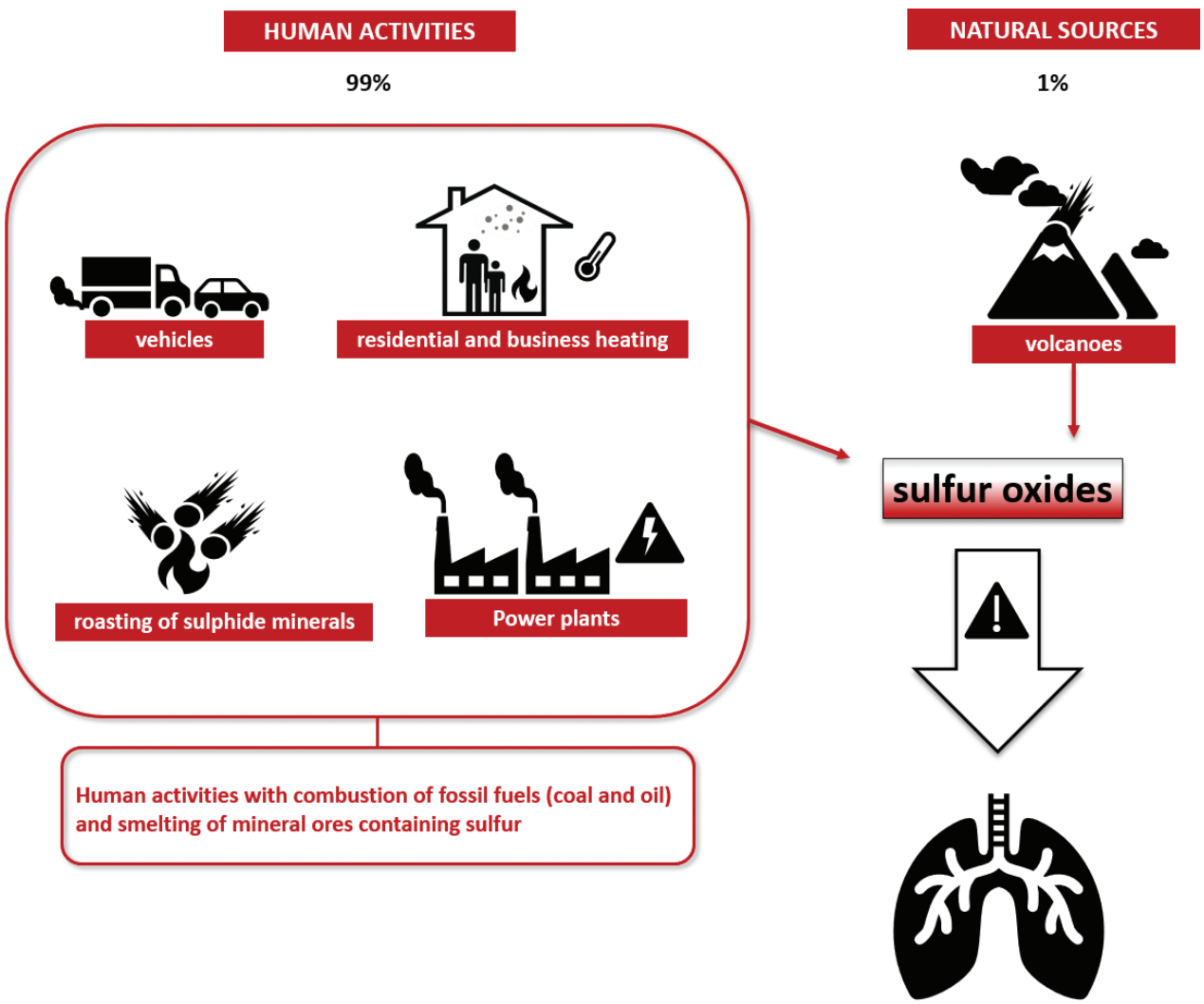

Figure 1 Sulphur Oxides Sources. Major sulphur dioxide sources are due to human activities, especially fossil fuel combustion, vehicles, roasting of sulphide minerals, other industrial activities, and -to a lesser degree- natural sources, namely volcanoes. The production of this harmful gas is dangerous for respiratory health.

In Europe the National Emission reduction Commitments (NEC) Directive established national commitments to cut emissions of five main pollutants, namely fine particulate matter (PM), nitrogen oxides (NO), nonmethane volatile organic compounds (NMVOCs), ammonia (NH) and sulphur dioxide (SO_2). Member States must meet emission reduction commitments for 2020-2029 and beyond, with the aim of reducing the number of premature deaths caused by air pollution and to preserve biodiversity. Despite economic growth, emissions have overall decoupled, with the most significant progress seen in SO, whose emissions showed the largest decrease of all pollutants. Nonetheless, while most Member States met their 2020-2029 commitments for SO emissions, some countries need significant further reductions to meet these targets.

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6 ENDOCRINE DISRUPTORS

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1. INTRODUCTION

The term "Endocrine Disruptors" (EDCs) was introduced in 1991 during the Wingspread Conference held at the Wingspread Conference Center in Racine, Wisconsin. During this gathering, experts from diverse fields agreed that "a significant array of synthetic chemicals" had been discharged into the environment and could dysregulate normal endocrine homeostasis by mimicking, blocking, or interfering with hormones in the body. United Nations Environment Program (UNEP) and World Health Organization defined EDCs as an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations. Key EDCs and their sources are presented in Table 1.

KEY MESSAGES

- EDCs can be found in places where we work and live (e.g., construction materials, floors, furniture, paints, pesticides), in products we make, grow, and buy (e.g., plasticizers, ink solvents, rubber, pesticides, insecticides, milk/water reusable bottles, household cleaning products, personal care products). Most of these chemicals are synthetic, although some occur naturally (e.g., phytoestrogens in soy foods)
- Exposure to EDCs can occur through different routes, such as ingesting food, water, soil, dust, inhalation, and absorption of chemicals through the skin (dermal contact). Some EDCs can also be transferred from mother to baby through the placenta and breast milk
- Exposure to EDCs or their combinations, even at minimal levels, particularly during critical developmental periods, can heighten the likelihood of allergic disease development. This occurs through the activation and amplification of proallergic immune responses, disruption of the epithelial barrier, encouragement of microbiome dysbiosis, and interference with endocrine functions. Additionally, such exposure may trigger dysautonomic activity, further exacerbating the risk of allergic diseases
- The impact of climate change has added pressure to the rising problem of EDCs since climate change may influence the rate at which EDCs are released from plastic materials and increase the (re-)emissions of persistent organic pollutants in different environmental settings

2. ENVIRONMENT, EXPOSURE, AND MECHANISMS

Evidence has demonstrated that changing environmental exposures over time and age are associated with developing allergic diseases and worsening symptoms. Among these concerning exposures are synthetic EDCs that are ubiquitous in today's modern society. EDCs are widely found in places where we work and live, things we make, grow, and buy. Although ingestion of contaminated food and beverages has been pointed out as the major route of exposure to EDCs, current evidence suggests that there is also chronic and sustained exposure to EDCs through inhalation and dermal contact. Maternal exposure to EDCs can also be transmitted to fetuses and infants through the placenta, umbilical

TABLE 1

List of key EDCs and their uses

Key EDCs	Sources or uses
Atrazine	Herbicides often used to control weeds in corn, sorghum, and sugarcane crops
Bisphenols (BPA, BPS, BPF)	Plasticizers (PVC and epoxy resins), food containers, building materials, manufacturing, toys, canned foods and beverages
Dioxins	Industrial by-products (herbicide production and paper bleaching) can be released into the air from waste burning and wildfires
Perchlorate	Industrial chemicals to make rockets, explosives, and fireworks which can be found in some groundwater
Per- and poly-fluoroalkyl substances (PFAS)	Repellents and coating for cookware, firefighting foam, nonstick pans, paper, textiles, and carpets
Phthalates	Plasticizers, consumer products (for example, cosmetics (nail polish, hair spray, aftershave lotion, cleanser, shampoo), fragrances, medical material), food packaging, children's toys
Phytoestrogens	Naturally occurring substances with hormone-like activity, present in soybean, sesame seeds, oats
Polybrominated diphenyl ethers (PBDE)	Furniture foam and carpet
Polychlorinated biphenyls (PCBs)	PCBs were mass-produced globally until they were banned in 1979. Electrical equipment, such as transformers, hydraulic fluids, heat transfer fluids, lubricants, and plasticizers
Triclosan	Antimicrobial and personal care products, such as liquid body wash and soaps

PVC, polyvinyl chloride

cord blood, and breast milk (Figure 1). Recent epidemiological and experimental studies have provided evidence of the mechanisms by which EDCs may increase the risk of developing allergic diseases, including activation and upregulation of proallergic immune processes, DNA methylation and epigenetic regulation of genes associated with immune pathways, such as the microtubule affinity regulating kinase 1 (MAPK1) and thymic stromal lymphopoietin (TSLP), disruption of the epithelial barrier, changes in microbiome composition and/or diversity, endocrine disruption, and changes in the autonomic nervous system (ANS) activity (Figure 1, 2).

3. CLINICAL IMPLICATIONS

EDCs pose a significant risk not only to public health but also to the health of our planet. Ubiquitous in our environment - found in foods, packaging materials, cosmetics, drinking water, and various consumer products - EDCs have been associated with a multitude of non-communicable diseases, spanning child and adult obesity, impaired glucose tolerance, gestational diabetes, reduced birthweight, compromised semen quality, polycystic ovarian syndrome, endometriosis, and breast cancer. Additionally, research suggests correlations between bisphenols and adult-onset diabetes, decreased semen quality, and polycystic ovarian syndrome; phthalates and premature birth, childhood obesity and asthma, and impaired glucose tolerance; organophosphate pesticides and diminished semen quality; and occupational exposure to pesticides and prostate cancer. Table 2 presents an overview of systematic reviews and meta-analyses to assess the association between EDC exposure and allergic diseases. Briefly, exposure to phthalates increased asthma risk by up to 41%, even when exposure occurred prenatally. Additionally, perfluoroalkyl substances were associated with higher risks of eczema, atopic dermatitis, and allergic rhinitis.

While systematic assessment is required to gauge the likelihood and strength of these connections, the accumulating evidence underscores the critical imperative to take immediate action to mitigate exposure to EDCs.

4. REDUCING EXPOSURE

Reducing exposure to harmful substances should be a top priority, utilizing various strategies. Government interventions, though limited, have proven effective in some cases, resulting in reduced disorders in humans and wildlife. The fifth International Conference on Chemicals Management (ICCM5) concluded successfully on September 30, 2023, in Bonn, Germany, with the adoption of the "Global Framework on Chemicals (GFC) – For a planet free of harm from chemicals and waste." This framework replaces the Strategic Approach to International Chemicals Management (SAICM), which failed to achieve its goal of ensuring responsible chemical management by 2020. SAICM's shortcomings prompted the development of the new framework, marking a significant milestone in

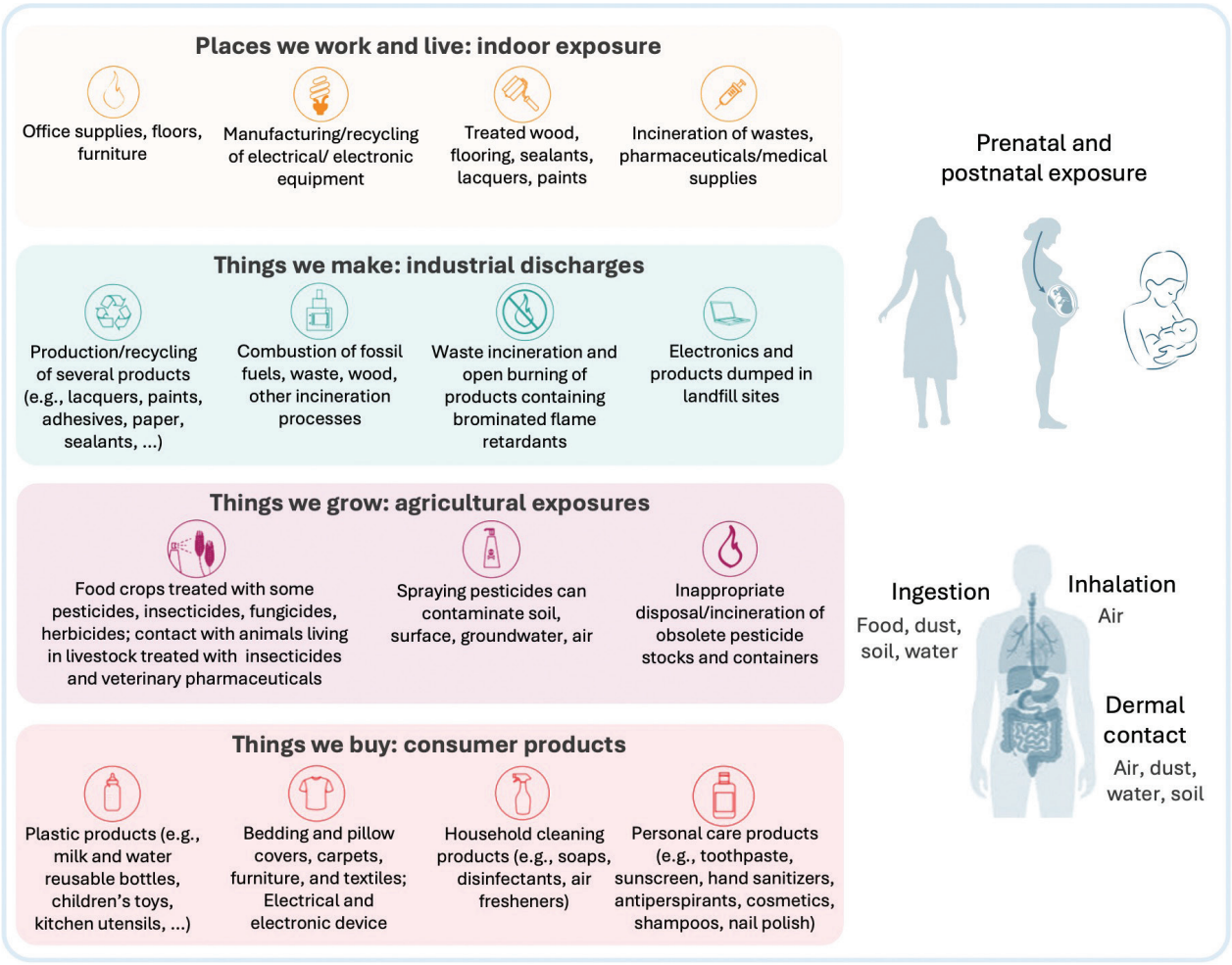

Figure 1 Sources and routes of exposure to EDCs.

global efforts for a toxic-free planet. The Bonn Declaration recognizes that chemical pollution causes millions of deaths, illnesses, and disabilities annually. It emphasizes the importance of managing chemicals and waste in alignment with the Paris Agreement on climate and the goals of the Kunming-Montreal Global Biodiversity Framework. The declaration commits to preventing exposure to harmful chemicals, phasing out the most hazardous substances, and safeguarding human rights for present and future generations (Figure 3).

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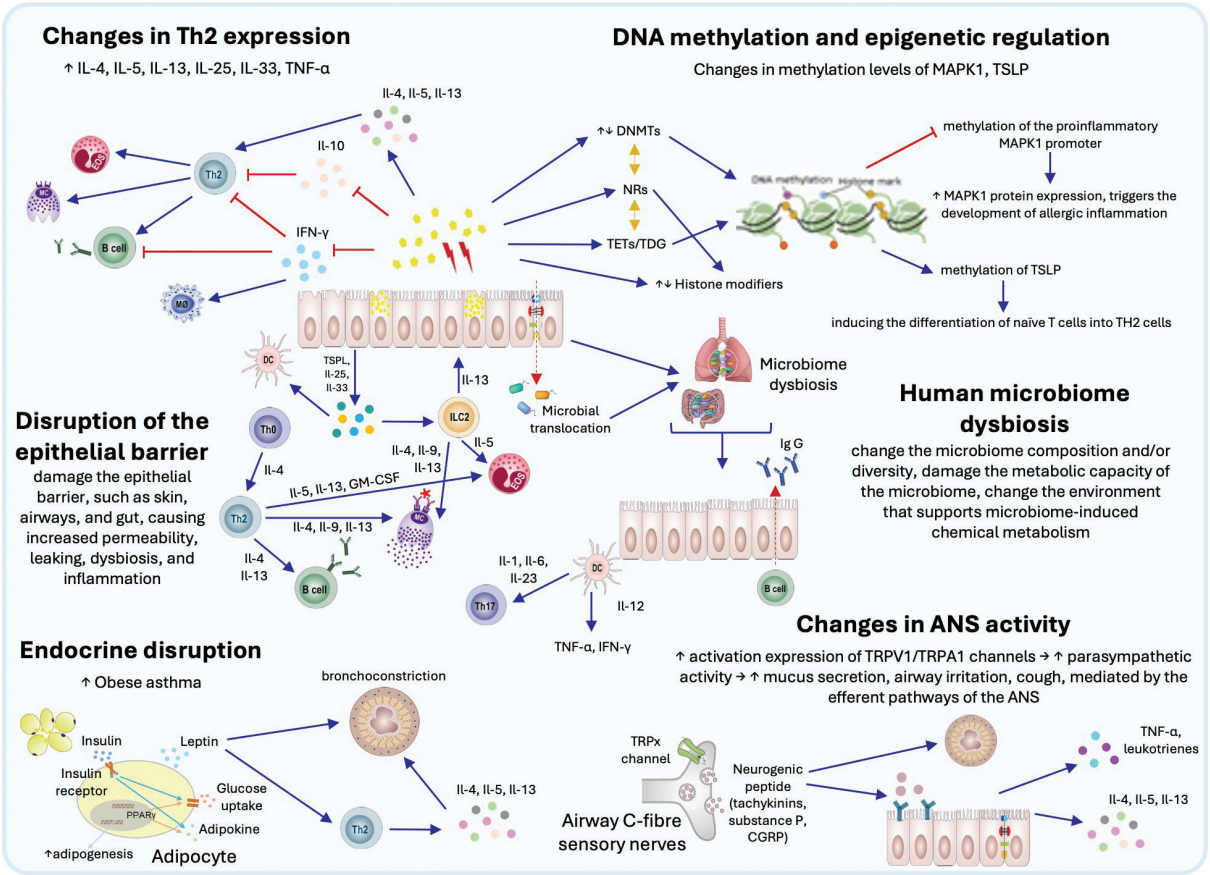

Figure 2 Potential underlying mechanisms for the effects of exposure to EDCs on allergic diseases.

Figure 3 World and population-level responses for mitigating and preventing exposure to harmful EDCs.

TABLE 2

Overview of systematic review and meta-analysis to assess the association between EDCs exposure and allergic diseases.

Reference	Exposure	Outcome	Results
Jaakkola and Knight, 2008 (1)	Phthalates	Asthma and allergies	In adult studies (n=10), a correlation emerged between exposure to heated PVC fumes and asthma. Among children (n=5), a significant association was observed between PVC surface materials in the home and the risk of asthma (OR 1.55; 95% CI: 1.18-2.05; based on four studies), as well as allergies (OR 1.32; 95% CI: 1.09-1.60; based on three studies).
Ming-Chieh Li et al., 2017 (2)	Phthalates: Benzyl butyl phthalate (BBzP), di-2-ethyl-hexyl phthalate (DEHP)	Childhood asthma	Metanalysis of 9 studies showed asthma and exposure to BBzP ORs increased from 1.39 to 1.41 across various combination strategies. Compared to postnatal exposure, prenatal exposure to BBzP was associated with an OR of 1.38 (95%CI: 1.09-1.75). Additionally, higher levels of di-2-ethylhexyl phthalate (DEHP) in dust were linked to a 2.71-fold increase in risk (95%CI: 1.39-5.28), along with a 2.08-fold increase in risk associated with BBzP (95%CI: 1.10-3.92)
Weixiang Wu et al., 2020 (3)	Phthalate: mono-benzyl phthalate (MBzP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP)	Asthma	Metanalysis of 14 studies highlighted an association between asthma and various phthalates. Specifically, elevated levels of MBzP had OR: 1.17; 95%CI: 1.06-1.28), MEHHP had OR: 1.13 (95%CI: 1.03-1.24), and MECPP exhibited an OR of 1.20 (95%CI: 1.00-1.42). Children with elevated levels of MBzP or mono-(carboxynonyl) phthalate (MCNP) were indicated to have heightened odds of asthma compared to older populations. Urinary levels of MBzP, MEHHP, MECPP, MCNP, and DEHP were positively related to asthma risk
Yuehua Luo et al., 2020 (4)	Perfluoroalkyl substances (PFASs)	Childhood allergic diseases	The meta-analysis comprising 13 studies revealed distinct associations between various perfluoroalkyl substances and allergic conditions. Specifically, perfluorononanoic acid (PFNA) demonstrated a correlation with eczema (OR=0.89; 95%CI: 0.80-0.99), while perfluorooctanesulfonic acid (PFOS) exhibited an association with atopic dermatitis (OR=1.26; 95%CI: 1.01-1.58), and perfluorooctanoic acid (PFOA) was linked to allergic rhinitis (OR=1.33; 95%CI: 1.13-1.56). No significant associations were observed for wheezing and asthma across the studies included in the analysis.
Minyoung Jung et al. (5)	Prenatal exposure to phthalate	Childhood atopic dermatitis (AD)	The meta-analysis comprising 8 studies revealed an association between monobenzyl phthalate (MBzP) exposure and the risk of AD development (OR: 1.16; 95%CI: 1.04-1.31). No associations were observed between AD development and other phthalate metabolites, including mono-(2-ethylhexyl) phthalate, monoethyl phthalate, mono-isobutyl phthalate, mono-n-butyl phthalate, and the sum of di-[2-ethylhexyl] phthalate
Alicia Abellan et al. 2021 (5)	Prenatal exposure to bisphenol A (BPA), bisphenol F (BPF), and bisphenol S (BPS)	Asthma, wheeze, and lung function in school-age children	In utero exposure to BPA correlated with increased odds of current asthma among girls (OR=1.13, 95%CI: 1.01, 1.27) and wheezing (OR=1.14, 95%CI: 1.01, 1.30). However, this association was not observed with overall wheezing patterns or lung function or among boys.
Ning Tang et al., 2022 (6)	Prenatal exposure to Bisphenol A (BPA) and triclosan (TCS)	Childhood allergic diseases	Meta-analysis involving 7 studies revealed a significant association between BPA exposure and an increased risk of various allergic diseases. Specifically, the odds ratios (OR) were 1.18 (95%CI: 1.02, 1.36) for wheezing, 1.23 (95%CI: 1.01, 1.50) for asthma, 1.03 (95%CI: 0.89, 1.18) for eczema/rashes or hives, and 1.19 (95%CI: 0.91, 1.56) for aeroallergies. However, prenatal exposure to TCS (triclosan) did not show any significant association with the four types of allergic diseases in childhood.

Search strategy: (PBDE OR brominated OR organophosphate OR chlorpyrifos OR POP OR phthalate OR DEHP OR BBP OR DBP OR DiBP OR phenol OR bisphenol OR BPA OR BPS OR BPF OR triclosan OR triclocarban OR benzophenone OR PFAS OR PFOA OR perfluoroalkyl OR perfluor OR perfluorinated OR pyrethroid OR parabens OR paraben* OR phytoestrogen OR nonylphenol OR "endocrine disruptor*") AND (asthma* OR allerg*) AND (systematic review OR Meta-analysis)*

7 EPITHELIAL BARRIERS AND AIR POLLUTION

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Air pollution, together with climate change, have an immense effect on human health. According to the World Health Organization, 91% of the world's population lives in poor air quality areas. Outdoor and indoor air pollution causes 3.7- 4.2 and 2.9-4.3 million annual fatalities, respectively. Air pollution plays a major role in the development and exacerbation of chronic obstructive pulmonary disease, asthma, chronic rhinosinusitis, allergic rhinitis, cardiovascular and neurodegenerative diseases.

Air pollution is a mixture of gaseous and particulate components, including ozone, sulfur dioxide, carbon monoxide, nitrogen oxides, particulate matter (PM), and volatile organic compounds such as formaldehyde (Table 1). The onset of asthma has been linked to exposure to specific traffic-related air pollution compounds such as black carbon, NO_2, PM, cigarette smoke. Furthermore, exposure to wildfire PM has been associated with an elevated risk of respiratory tract infections, asthma, and chronic obstructive pulmonary disease, as well as increased hospital admissions and emergency room visits.

KEY MESSAGES

- Air pollution causes several millions of fatalities worldwide
- It plays a significant role in the pathogenesis of respiratory, cardiovascular and neurodegenerative diseases
- Air pollutants are a complex mixture of components, such as ozone, SO_2, CO, NO, NO_2, micro and nanoplastics, volatile organic compounds, particulate matter, and diesel exhaust particles
- Exposure to air pollutants causes epithelial cell and immune system activation, reactive oxygen species formation, cell death, inflammation, and epithelial barrier impairment

Exposure to air pollutants triggers the production of reactive oxygen species (ROS) and compromises the epithelial barrier integrity. In addition, they have a detrimental effect on the microbiome. The symbiotic relationship between the microbiota in the airways and the host is crucial for maintaining epithelial barrier integrity and immune tolerance in the airways. Anthropogenic PM, particularly secondary organic aerosols from residential biomass burning and non-exhaust emissions from vehicles, possess increased oxidative potential. PM is known to induce various forms of cell death, including apoptosis, necrosis, pyroptosis, and causes autophagy. Cell death and cellular stress cause the release of epithelial alarmins such as IL-25, IL-33, and thymic stromal lymphopoietin. This marks the initiation of epithelitis characterized by epithelial cell death and inflammation. PM disrupts the airway epithelial barrier, compromises tolerance to inhaled substances, and increases sensitivity to allergens. $PM_{2.5}$ exposure adversely affects lung function in mice, leading to reduced total lung capacity, residual volume, and vital capacity. It triggers apoptosis, reduces the expression of tight junction proteins, and promotes airway inflammation through NF-κB and MAPK activation. Additionally, $PM_{2.5}$ exacerbates asthma in mouse models of allergic asthma (Figure 1).

Volatile organic compounds, such as ozone, nitrogen oxides, formal-

TABLE 1

Ambient and indoor air pollutants		
Particulate matter 2.5		Radon
Particulate matter 10		Lead
Carbon monoxide		Black carbon
Ozone		Ultrafine particles
Nitrogen dioxide		Benzene
Sulfur dioxide		Trichloroethylene
Formaldehyde		Tetrachloroethylene
Polycyclic aromatic hydrocarbons		Naphthalene

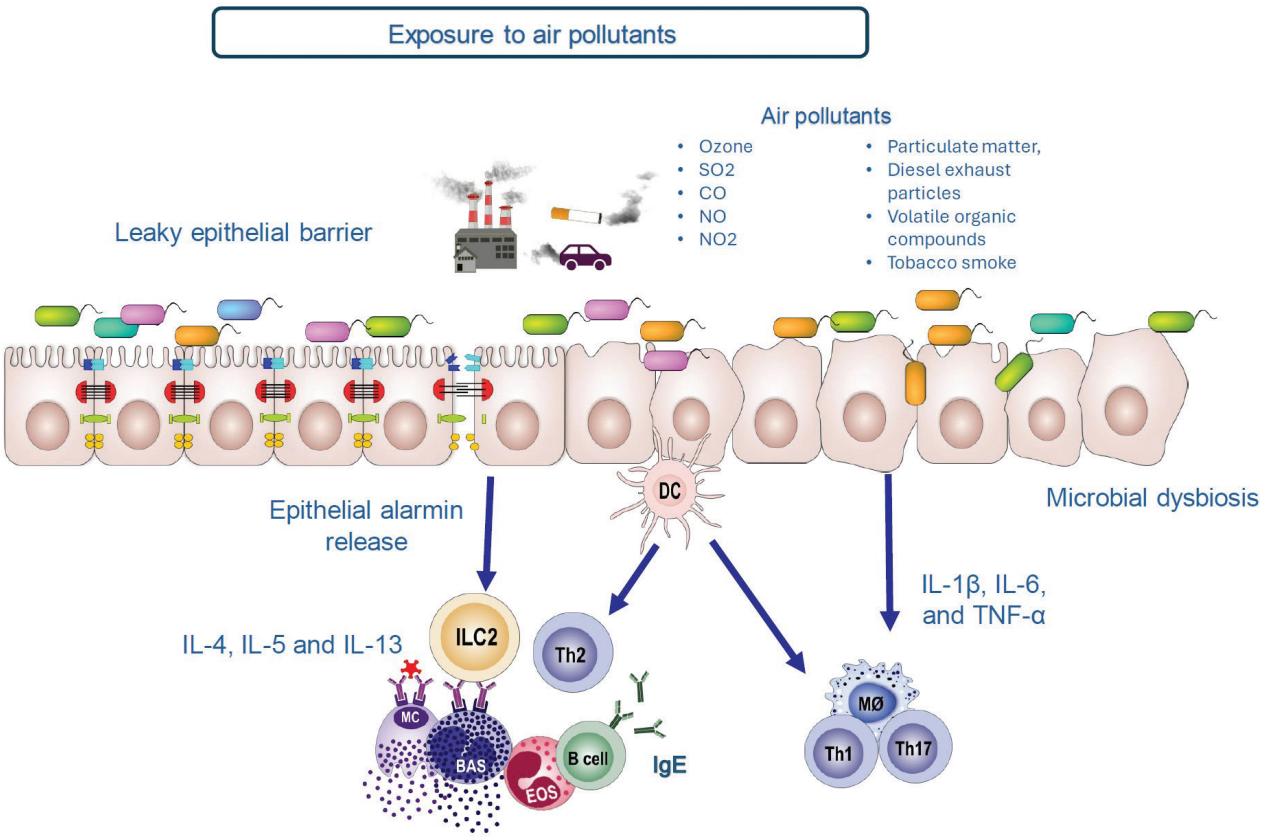

Figure 1 Air pollutants such as particulate matter, volatile organic compounds, ozone, and nitrogen oxides cause epithelial microbial dysbiosis, epithelial barrier impairment, and inflammation. Cellular stress and reactive oxygen species caused by air pollutants induce apoptosis, necrosis, pyroptosis, and autophagy. This results in epithelial alarmin release, proinflammatory cytokine release, and immune cell activation. BAS, basophil; DC, dendritic cell; EOS, eosinophil; IL, interleukin; ILC2, innate lymphocyte 2; M, macrophage; MAPK, mitogen-activated protein kinases; MC, mast cell; NF-κB, nuclear factor 'kappa-light-chain-enhancer' of activated B-cells; ROS, reactive oxygen species; Th1, type 1 T cell; Th17, type 17 T cell; Th2, type 2 T cell; TSLP, thymic stromal lymphopoietin.

dehyde, acetaldehyde, toluene, and xylene, cause epithelial barrier impairment. Interestingly, Nitrogen dioxide pollution contributes to approximately 4 million new pediatric asthma cases annually and an increased risk of atopic eczema in adult males. Coexposure to ozone and carbon black results in decreased lung function, inflammation, and necrosis of bronchiolar epithelial cells.

Controlling air pollution is essential to prevent chronic inflammatory airway diseases, cardiovascular diseases, and allergic conditions. Therefore, it is important to maintain both ambient and indoor air pollution levels at guideline values by implementing adequate policies and procedures.

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8

CO_2 EXPOSURE AND DISEASES

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KEY MESSAGES

- Elevated levels of atmospheric CO_2 and subsequent global warming pose major threats to human health in multiple ways
- Increasing atmospheric CO_2 may alter the morbidity and severity of the diseases and the allergenicity of pollen
- Understanding the molecular mechanisms and global health impacts of elevated indoor CO_2 levels is essential

Elevating levels of atmospheric CO_2 and progressing global warming pose direct and indirect threats to human health physically and mentally. Globally increasing CO_2, in combination with rising temperatures, induces climate changes and changes in nature, for example, increasing pollen allergenicity and migrating allergens and infectious diseases to another area (Figure 1). Pollen allergens possess the capability to induce the release of pro-inflammatory and immunomodulatory mediators. It has been reported that elevated levels of ambient CO_2 increase allergenicity depending on the interplay of multiple metabolites and elicit a stronger allergic response *in vivo* and *in vitro*. In addition, rising ambient temperatures affect increased morbidity and mortality of major neurological disorders. Notably, CO_2 exposure has significant neurological effects as inhalation of 35% CO_2 has been established to elicit fear and panic attacks. Moreover, studies demonstrated a direct impact of high ambient temperatures inhibiting inflammasome-dependent cytokine secretion and respiratory dendritic cell migration to lymph nodes. Furthermore, CO_2 itself also cause health problems. Long-term exposure of mice to high CO_2 (890 ppm) resulted in respiratory impairments, altered growth patterns in early life and showed hyperactive behaviours.

CO_2 is one of the indoor air pollutants. According to the WHO, household air pollution contributes significantly to global mortality, with approximately 3.2 million deaths annually. Stroke, ischaemic heart disease, lower respiratory infections, chronic obstructive pulmonary disease (COPD), and lung cancer collectively account for most of these deaths. CO_2 concentrations are increased in relation to the perception of human bio-effluents, especially in the closed workplace. In addition, cooking and smoking affect the elevation of indoor CO_2 levels. The United States Occupational Safety and Health Administration (OSHA) and National Institute for Occupational Safety and The American Conference of Governmental Industrial Hygienists (ACGIH) recommend 5,000 ppm (0.5%) as a limit for an 8-hour exposure and 30,000 ppm (3 %) for a short term (10-minute) period (Carbon Dioxide Health Hazard Information Sheet). Although CO_2 is considered as minimally toxic by inhalation, a study with mice showed that 2000 to 4000 ppm CO_2 exposure for 2 hours triggers neutrophils to generate microparticles containing high concentrations of IL-1β that cause diffuse inflammatory vascular injury. The significant increase in atmospheric CO_2 is mainly due to the burning of fossil fuels from power plants, factories, and transportation. Smoking, cooking, and closed-room conditions also contribute to the increasing indoor CO_2 (Figure 2). Green plants are the primary

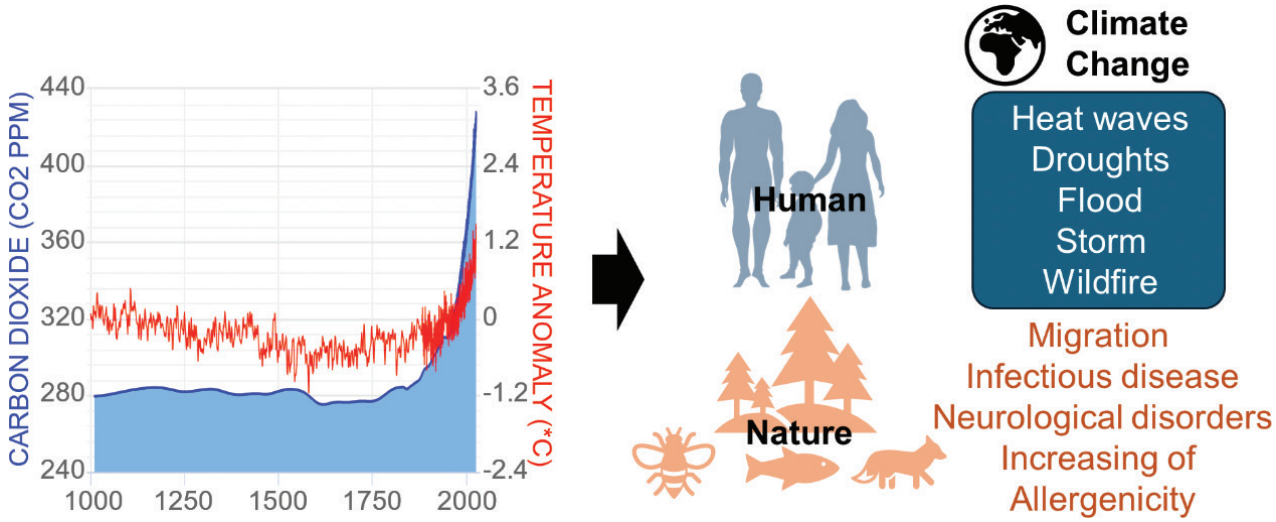

Figure 1 Increasing global CO_2 levels and temperature affect human and natural health. The figure from www.co2levels.org is modified

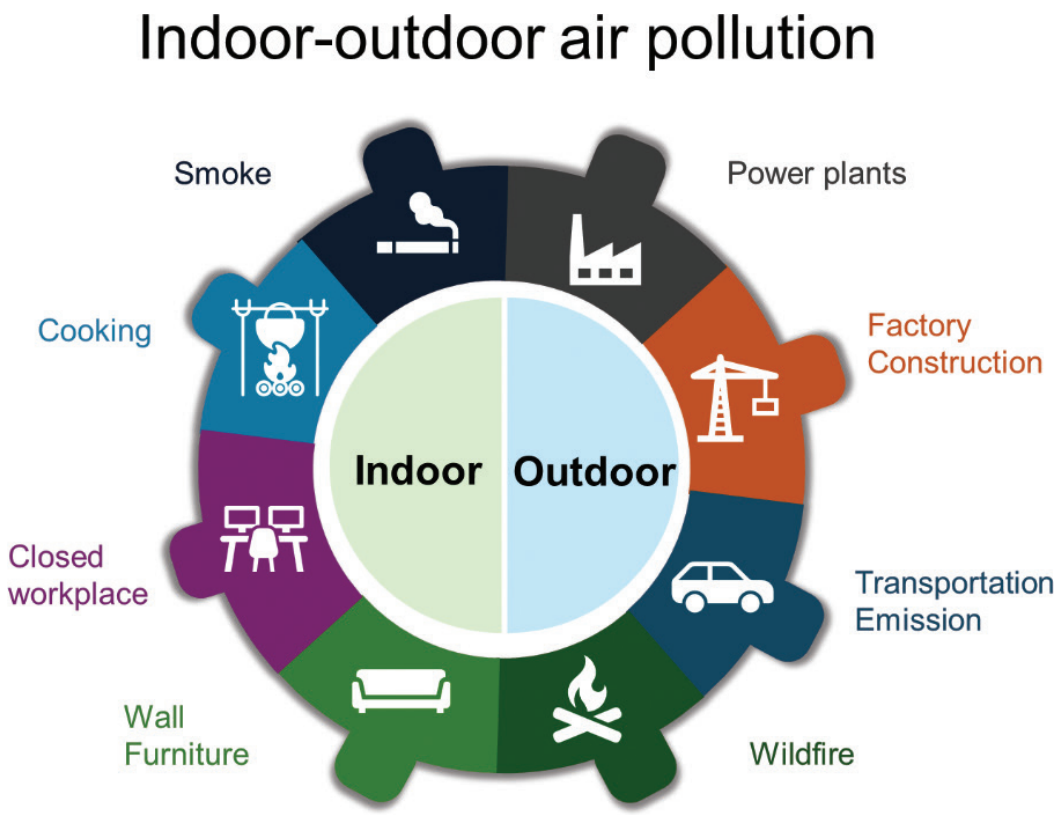

Figure 2 Effects of increasing atmospheric CO_2.

consumers of CO_2 through photosynthesis, which helps reduce atmospheric CO_2 levels. It is limited mainly during daylight hours.

The risk of increasing CO_2 levels to global health is still unclear as the outdoor levels are by far below the tolerable risk levels, however indoor CO_2 especially in patient rooms at night exceeds to 2000 ppm, which may show health effects. We must determine the impact of increasing outdoor and indoor CO_2 on public health.

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9 EPITHELIAL BARRIER THEORY AND LAUNDRY DETERGENTS

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KEY MESSAGES

- Laundry detergents and their main ingredient, sodium lauryl sulfate, causes epithelial cell toxicity and barrier dysfunction
- Detergent-induced oxidative stress and barrier damage initiate type 2 inflammatory diseases
- The detergent exposure may be related to the increasing allergic and inflammatory diseases

The development of synthetic detergents began in the early 20th century because of the shortage of soap during World War I. The household cleaning product containing synthetic detergents was developed in 1946 and became popular among consumers after 1960s. Synthetic surfactants have been increasingly incorporated into household products as detergents. Sodium dodecyl sulfate also called sodium lauryl sulfate (SDS/SLS) is commonly added to detergents for its surfactant properties, which effectively removes dirt and grease. However, with increasing occupational and daily exposure to detergents (Figure 1), and increased numbers of occupational rhinitis, asthma and dermatitis, concerns arise regarding the potential health issues associated with these products.

Laundry detergents are typically composed of a complex mixture of 30 to 70 different molecules, each working to tackle stains by various means, including water softening, alteration of surface tension through surfactants, and enzymatic degradation of proteins (Figure 2). Despite their widespread usage, there is no international standardization for the dosage of these potentially harmful substances.

Recent studies have demonstrated the cytotoxicity and epithelial barrier disruptive effects of laundry detergents on human skin keratinocytes and bronchial epithelial cells. In addition, the harmful proinflammatory and barrier disruptive effects of laundry detergents and SDS were reported *in vivo* and *ex vivo* human skin. Residues of laundry-detergent found in the household dust extracts and clothing rinse residues further underscore the potential for chronic exposure that may affect epithelial barriers.

Furthermore, SDS, a common ingredient found not only in detergents but also in other daily products such as toothpastes and dishwasher detergents may disrupt oral, esophageal, and gut epithelial barriers. Eosinophilic esophagitis (EoE) is another chronic type 2 inflammatory disorder with clinical manifestations including dysphagia, food impaction, and failure to thrive. Current research indicated that SDS exposure shows epithelial barrier dysfunction and exacerbates EoE symptoms in ALI-cultured esophageal epithelial cells and mouse models with 0.5 % SDS in drinking water. It has to be noted here that many toothpastes contain 3% SLS/SDS, included as an ingredient since 2000s, which is associated with the increased prevalence of eosinophilic esophagitis. Toxic doses of sles goes down to 0.002% and this dose is significantly less than a post rinse remnant. Moreover, laundry detergent-induced oxidative stress and subsequent type-2 inflammatory response suggest a potential link between detergent

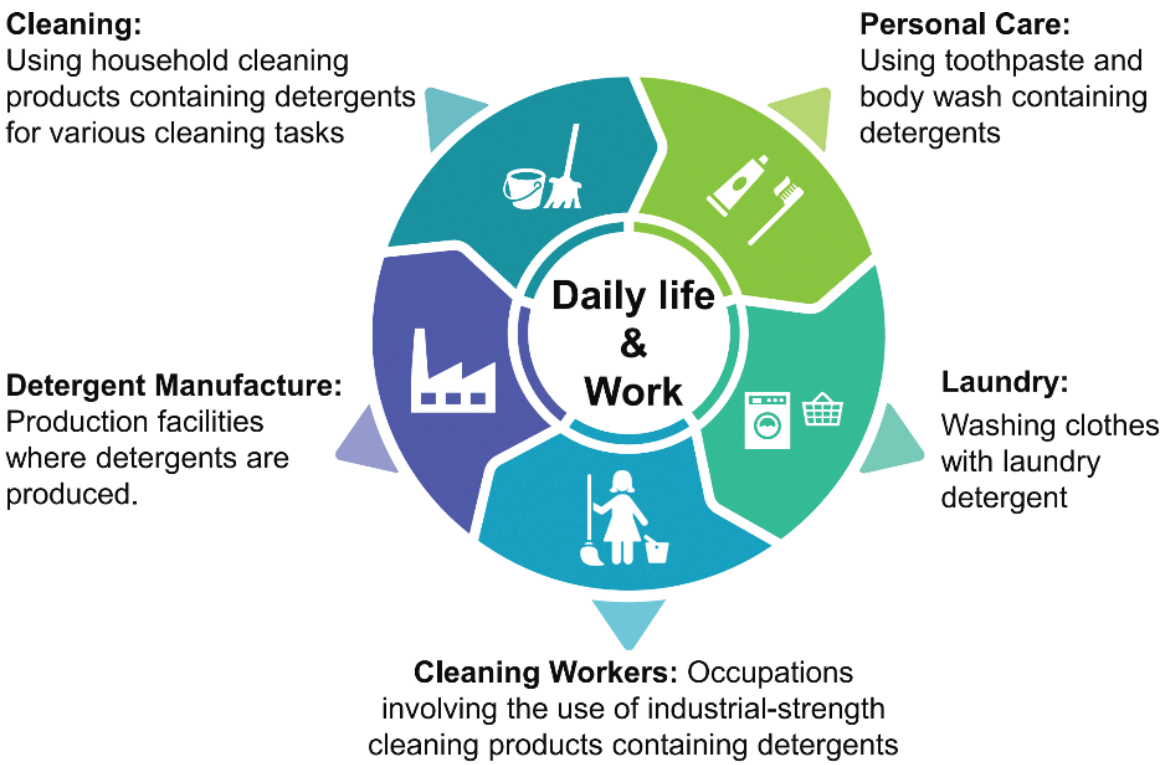

Figure 1 Occupational and daily exposure to the detergents. Risk factors in daily life and workplaces.

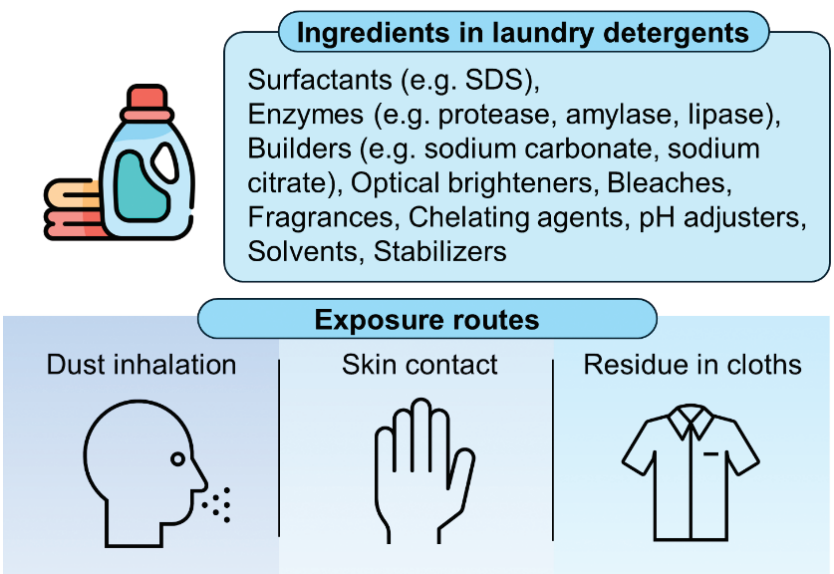

Figure 2 Ingredients in household laundry detergents and their exposure routes.

exposure and the eosinophilic airway inflammation via epithelial IL-33 alarmin production, barrier leakiness, ILC2 activation and their IL-5 and IL-13 release in mouse.

Beyond its direct effect on the epithelial barrier, detergents exacerbate skin inflammation, induced by protease with itch and robust T helper 17/T helper 22 differentiation. Additionally, occupational respiratory diseases are a serious problem in the detergent industry. A recent cohort showed that the reduced spirometry parameters was observed in detergent factory workers after 8 hours of shift work.

Exposure to daily laundry detergent and cleaning products presents a serious threat to human health, as evidenced by their cytotoxic, barrier-disruptive, and inflammatory effects on various epithelial barriers. Regulation and awareness regarding the potential health risks are crucial.

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10 EPITHELIAL INFLAMMATION, CELL DEATH AND BARRIER DAMAGING EFFECTS OF PROFESSIONAL DISHWASHING

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KEY MESSAGES

- In professional dishwashers, dishes undergo a one to two-minute washing cycle at 82°C and 4 atmosphere pressure, without any further rinsing after the application of rinse aid that dries on the dishes, glasses and cutlery
- The concentration of rinse aid typically utilized on daily basis ranges between dilutions of 1:2,000 and 1:10,000
- The disruption of epithelial barrier function in response to rinse aid exposure involves cell death at dilutions of 1:10,000 and epithelial inflammation and barrier opening at dilutions of 1:40,000
- The presence of alcohol ethoxylates in the rinse aid leads to epithelial inflammation and barrier impairment in gut-on-a-chips and induced pluripotent stem cell derived intestinal organoids

According to the epithelial barrier theory, exposure to toxic substances in humans and animals disrupts the integrity of the epithelium that lines the skin, lungs, and intestine. Impaired epithelial barriers in the gastrointestinal tract, coupled with dysbiosis in the gut microbiota, have been implicated in various diseases, including diabetes, obesity, non-alcoholic fatty liver disease, autoimmune hepatitis, liver cirrhosis, rheumatoid arthritis, multiple sclerosis, autism spectrum disorders, chronic depression, Alzheimer's disease, and Parkinson's disease. Additionally, the prevalence of allergic diseases, particularly food allergies and eosinophilic esophagitis, has increased dramatically since the 2000s.

As a consequence of industrialization and modernization, particularly since the 2000s, the utilization of professional dishwashing has become increasingly common. The convenience of saving time and the assurance of hygienic cleanliness have led to a significant increase in the daily utilization of professional dishwashers, particularly in public food service settings such as restaurants, schools, military facilities, hospitals and hotels.

Professional dishwashers typically operate by circulating approximately 3-4 liters of water heated to a minimum of 65°C, with the addition of detergent, for a duration of up to 60 seconds under 2 to 4 atmosphere pressure. Subsequently, a rinse/dry cycle ensues, involving the introduction of 3-4 liters of water heated to at least 82°C along with the application of rinse aid. These cycles, collectively lasting between 60 to 120 seconds depending on the specific type of professional dishwasher, aim to achieve a thorough cleaning and sterilization of dishes, glasses, and cutlery. There is no further rinse at the last step and the remaining substances are not washed away and dry on the surfaces of dishes, glasses and cutlery.

Recently, it has been reported that rinse aids and particularly due to their alcohol ethoxylate content have significantly toxic and disruptive effects on the barrier integrity, innate immune response and proinflammatory transcription factors of gut epithelial cells with altering the mRNA expression of a high number of genes and protein expressions (Figure 1). Although the allowed dilution factor is between 1:2000 and 1:10,000 even

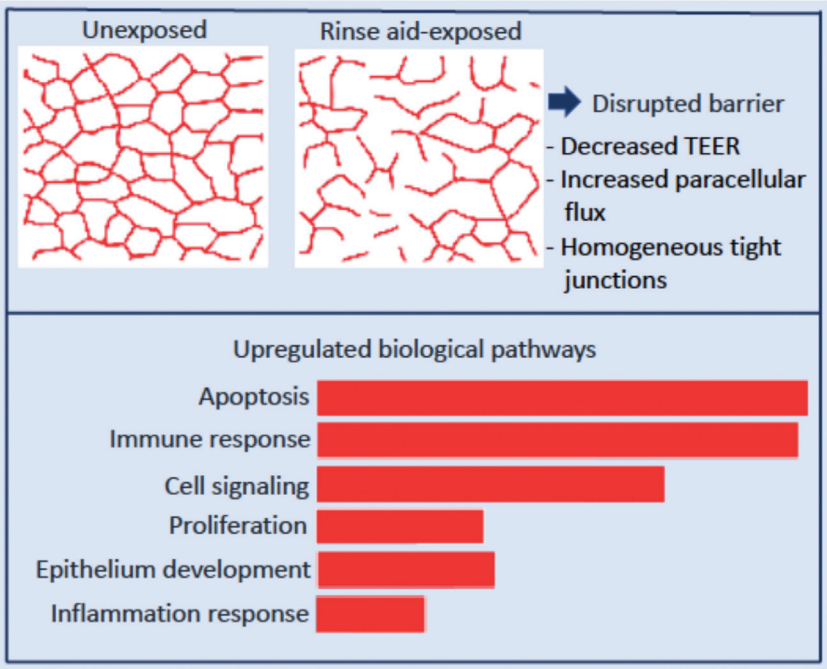

Figure 1 Rinse aid directly impairs barrier integrity of gut epithelial cells and causes toxicity and inflammatory and immune responses, and upregulates some biological pathways at daily used concentration.

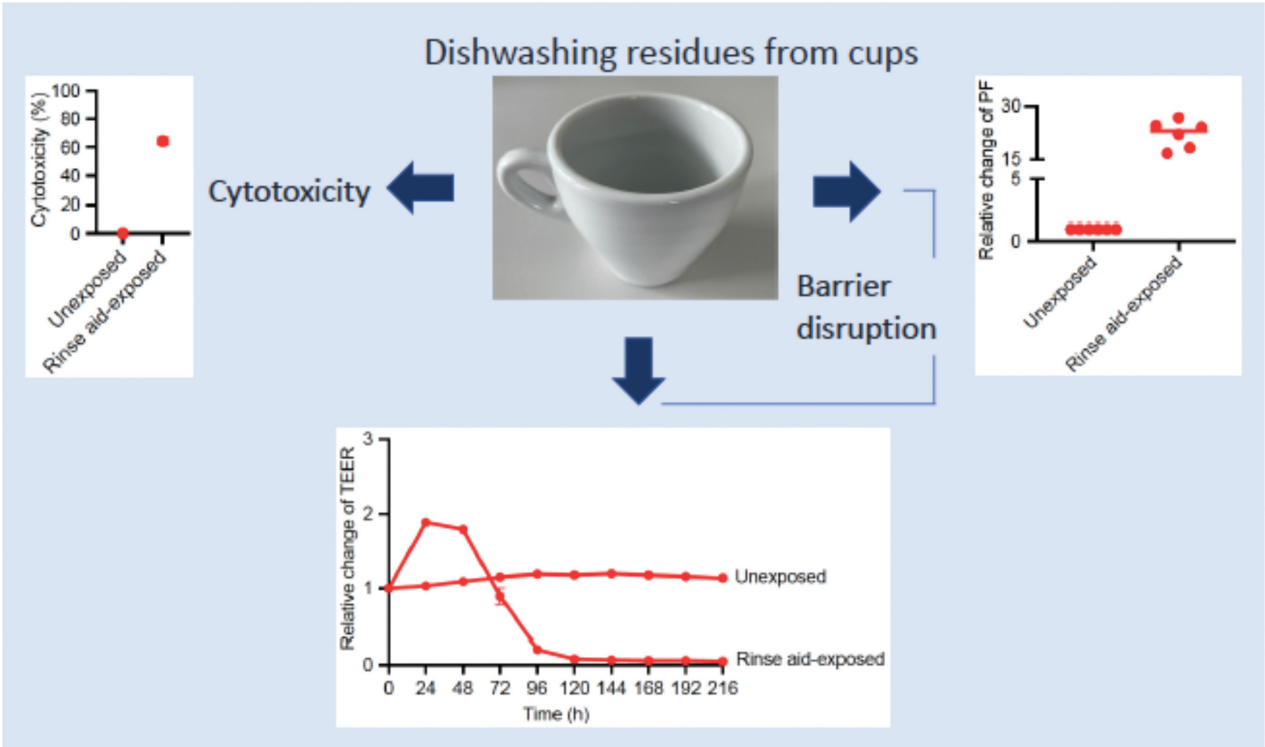

Figure 2 Dishwashing residues on a cup after washing in professional dishwasher shows cytotoxic and barrier disruption effects on gut epithelial cells.

1:40,000 dilutions affected many mRNAs and proteins in this respect. The expression of genes involved in cell survival, epithelial barrier, immune and inflammatory responses, and metabolism were altered upon cell exposure to rinse aid concentrations typically used in professional dishwashers (Figure 1). Interestingly, detergent residue from professional dishwashers demonstrates the presence of a significant amount of cytotoxic and epithelial barrier damaging rinse aid remaining on washed and ready to use dishware (Figure 2). Assuming that a chronic exposure and exposure to other epithelial barrier damaging substances at the same time will take place, utmost attention should be paid that exposure to toxic doses of rinse aid is strictly controlled, especially in restaurants, schools, armies and hotels.

It is now essential to tackle this issue by the regulatory authorities and find non-toxic rinse aids and washing protocols.

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11 NON-NUTRITIVE SWEETENERS AND EPITHELIAL BARRIERS

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KEY MESSAGES

- The replacement of sugar with non-nutritive sweeteners (NNS) is a common strategy worldwide for weight loss, weight maintenance, and managing diabetes
- NNS can alter intestinal microbiota, and have negative effects on intestinal barrier permeability, potentially allowing increased passage of bacterial products that may contribute to metabolic disorders and inflammatory disesases
- The increment of chronic inflammatory diseases, such as allergy and inflammatory bowel disease (IBD) are associated with the massive introduction of NNS in the daily food intake
- The awareness and education of public and regulatory authorities on the potential risks of NNS, and the exposure to harmful substances that are linked with the onset of inflammatory diseases is essential

The use of non-nutritive sweeteners (NNS) as an alternative to caloric sugars has increased significantly worldwide in recent decades. The main NNS approved for use include acesulfame-K, aspartame, neotame, saccharin, sucralose, and steviol glycosides (Table 1). These sweeteners are monitored by regulatory agencies to ensure their approval and safe levels of use (Table 1). However, the World Health Organization (WHO) has recently issued a guideline discouraging the use of NNS for weight management or to reduce the risk of non-communicable diseases, citing the potential adverse effects of long-term NNS use.

The intestinal epithelial barrier maintains selective permeability to allow for nutrient absorption while preventing the entry of pathogens and harmful molecules into circulation. Impairment of this barrier and increased intestinal permeability can lead to the development of chronic inflammatory diseases (Figure 1). Most NNS are not digested by the host and can interact directly with the gut microbiota, potentially altering the composition and function of the microbiome. Current evidence from rodent models suggests that exposure to NNS can alter the diversity and composition of the gut microbiome (Table 2). In co-culture experiments with human intestinal epithelial cells (Caco-2), bacteria exposed to NNS showed enhanced abilities to adhere, invade, and kill host epithelial cells. Dysbiosis affects the barrier permeability and homeostasis of the digestive system through a balance of immune response and tolerance between the host immune response and microbiota. Exposure to NNS in both mouse and human epithelial cell models has been shown to disrupt the intestinal epithelial barrier by de-regulating tight junction proteins (Table 2). Further studies are needed to fully understand the potential effects of NNS on the epithelial cell inflammation and barrier function using standardized protocols, at physiologically relevant doses, and to validate findings in human clinical trials.

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TABLE 1

Characteristics of commonly used non-nutritive sweeteners

Name (EU additive code)	Brand Names	ADI (mg/ml)	SI	Use
Saccharin (E954)	Sweet and Low®, Sweet Twin®, Sweet'N Low®, Necta Sweet®	5	300-500x	Beverages, bases, and mixes for many food products, table sugar substitute
Aspartame (E951)	Nutrasweet®, Equal®, Sugar Twin®	40	200x	Soft drinks, chewing gum, pudding, cereals, instant coffee
Sucralose (E955)	Splenda®	5	300-500x	Beverages, bases, and mixes for many food and medicine products
Acesulfame-K (E950)	Sunett®, Sweet One®	50	200x	Beverages, candy, frozen desserts, baked goods Heat stable so it can be used in baking
Steviol glycosides (E960)	Natural constituents of leaves of *Stevia rebaudiana* (Bertoni) plant, Stevia (Truvia®)	4	250-300x	Beverages, chewing gum, candy, table sugar substitute

EU, European Union; ADI, acceptable daily intake, established by the Food and Drug Administration (FDA), the European Food Safety Authority (EFSA), and the Joint FAO/WHO Expert Committee on Food Additives (JECFA); SI, sweetness intensity (relative to sucrose).

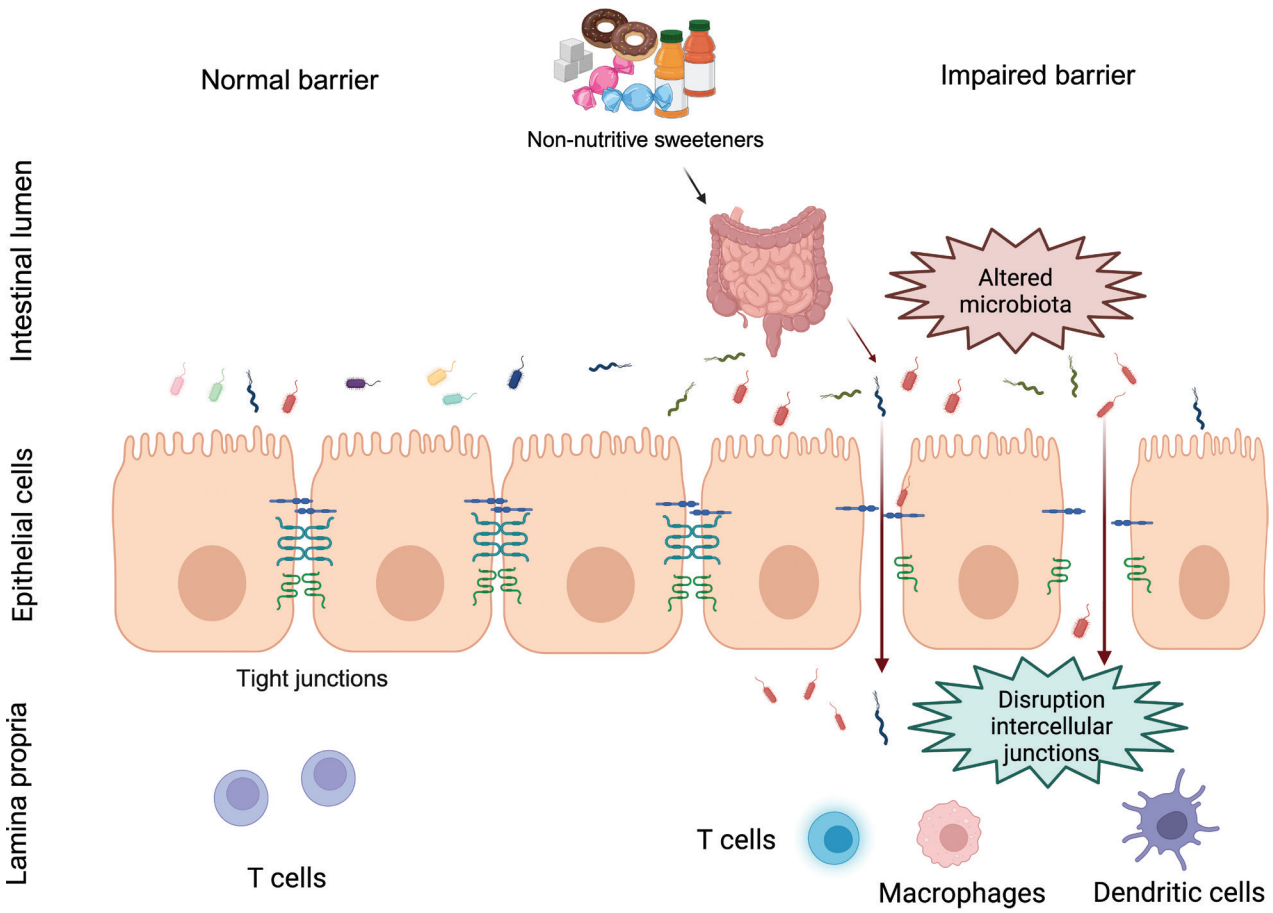

Figure 1 Effects of exposure to non-nutritive sweeteners on the gut epithelial barrier and microbiota. Non-nutritive sweeteners in the diet can disrupt the epithelial barrier and alter the gut microbiota leading to inflammatory activation.

TABLE 1

Non-nutritive sweeteners and their effects on gut microbiota and epithelial barrier

Name	Model	Microbiota	Barrier damage	Ref.
Saccharin	Mice	Reduction in bacterial diversity		3
	Human microbiota	Altered gut and oral microbiota		4
	Caco-2		Deregulation of claudin-1 via NF-kB	3
Aspartame	Human microbiota		Increased propionate and acetate production	3
	Rats	Alteration of gut microbiota		3
	Human microbiota	Altered gut and oral microbiota		5
	Caco-2		Increased permeability, disbalance of claudin proteins	5
Sucralose	Mice	Reduction in bacterial diversity		3
	Human microbiota	Increased *Escherichia/Shigella/ Bilophila*		3
	Mice	Gut microbiota changes	Alteration of gut barrier	3
	Mice	Gut dysbiosis	Decreased gut barrier integrity	3
	Mice	Gut dysbiosis		3
	Mice		Increased gut damage Increased permeability	3
	Mice	Reduced amount of *Clostridium* cluster XIVa		3
	Human microbiota	Altered gut and oral microbiota		4
	Caco-2		Increased permeability, disbalance of claudin proteins	5
	Lung endothelial cell and mouse model		Attenuated LPS barrier dysfunction *in vitro* and lung edema *in vivo*	6
Acesul-fame-K	Mice	Induced microbial changes	Induced intestinal injury with lymphocyte migration Increased intestinal permeability Decreased GLP-1R and GLP-2R expression	3
Neotame	Mice	Alteration of the microbial diversity	Decrease in expression of butyrate synthetic genes	3
Steviol glycosides	Mice	Improvement in bacterial diversity		3
	Human microbiota	Microbial diversity increased		3
	Human microbiota	Altered gut and oral microbiota		4

Acesulfame-k: Acesulfame potassium; GLP-1R, glucagon-like peptide-1/2 receptor; LPS, lipopolysaccharide.

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12 EPITHELIAL BARRIERS AND PROCESSED FOOD ADDITIVES

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KEY MESSAGES

- Diet and lifestyle choices may contribute to chronic inflammatory diseases by straining the protective gastrointestinal epithelial barrier
- The consumption of processed foods containing additives and emulsifiers correlate with the rise in conditions like inflammatory bowel disease, obesity, metabolic syndrome and diabetes
- Food emulsifiers cause “epithelitis”, release of alarmins and proinflammatory chemokines, disrupt the gut barrier, promote inflammation and contribute to chronic diseases
- Polysorbates are widely used emulsifiers in processed foods, disrupt the gut barrier integrity, cause cellular damage, oxidative stress and inflammation at legally allowed concentrations

The "epithelial barrier theory" suggests that harmful substances, introduced through a mixture of diet and lifestyle choices, strain the protective epithelial barrier. Since 1960s, more than 350,000 substances have been introduced to humans' life. From the mid-20th century onward, there has been a notable increase in the consumption of processed foods containing additives and emulsifiers. The commercial aim of their usage was to extend the shelf life and prevent the separation of the liquids and keeping the texture and consistency. This was achieved mostly after 2000s by using food additives, such as synthetic colorants, preservatives, stabilizers, surfactants, emulsifiers, and texturizers are frequently employed in processed foods. This trend aligns with a rise in the occurrence of several chronic inflammatory conditions, including Crohn's disease, ulcerative colitis, diabetes, obesity, and metabolic syndrome. Animal and human studies conducted *in vivo* indicated that increased consumption of ultra-processed foods was linked to a heightened risk of microvascular diseases like chronic kidney disease and inflammatory bowel disease. Moreover, regularly ingested food additives were found to affect anxiety-related and psychosocial behaviors.

Previous *in vitro* studies reveals that non-ionic surfactant food emulsifiers have concentration-dependent effects on intestinal cells such as increasing permeability, disturbing cell viability, promoting bacterial translocation across M-cells, damaging of mitochondria in enterocytes and enhancing allergen absorption. One of the most commonly used emulsifiers, polysorbates are a type of non-ionic surfactant, which serve to enhance the texture, and consistency. In addition, they act as emulsifiers, aiding in blending ingredients like oil and water.

Table 1

List of food emulsifiers that are shown to affect epithelial cells and microbiome
Polysorbate 20 (E432)
Polysorbate 80 (E433)
Carboxymethyl cellulose (E466)
Guar gum (E412)
Carrageenans gum (E407)
Acetyl tartaric acid esters of mono-glycerides and diglycerides of fatty acids (E472e)
Xanthan gum (E415)
Lecithins (E322)

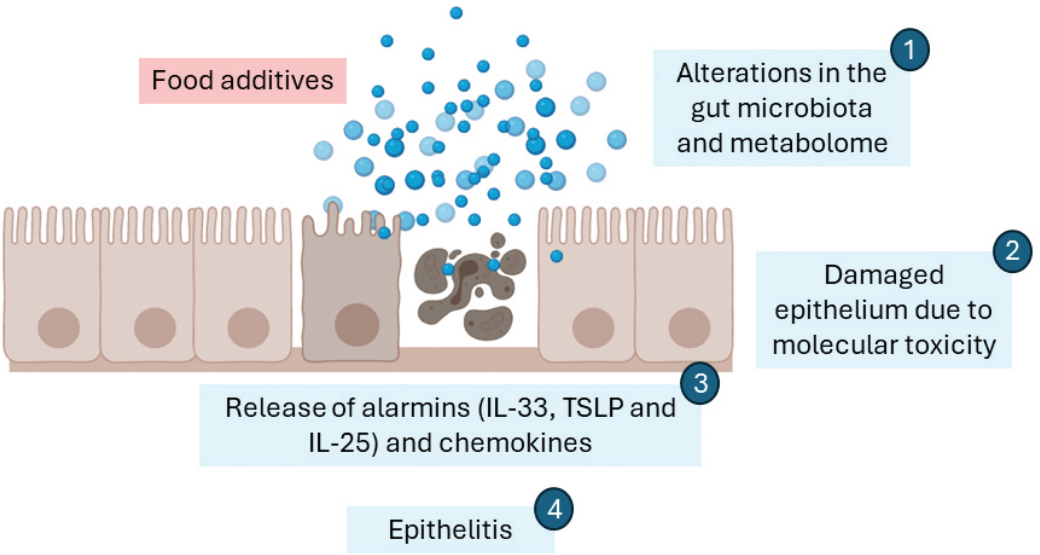

Figure 1 What happens when epithelial barriers expose to food additives? Food additives may alter gut microbiota and disrupt the epithelial barrier due to the molecular toxicity. In addition, epithelial injury stimulates the release of alarmins, IL-33, TSLP and IL-25 and many chemokines that activate the innate lymphoid cells, dendritic cells, macrophages and T and B cells to initiate the inflammation. Increased inflammation may accelerate the barrier damage more, promote bacterial translocation, enhance allergen absorption and eventually cause the cell death.

They're prevalent in various processed foods such as ice cream, baked goods, salad dressings, and sauces, typically at concentrations up to 1%. Studies employing human models, including induced pluripotent stem cell-derived human intestinal organoids, colon organoids, organs-on-a-chip, and liquid-liquid interface cultures, have revealed that P20 and P80, two common polysorbates, disrupt the gut epithelial barrier. This disruption results from cell death, molecular toxicity, and the activation of genes and proteins that provoke inflammatory responses in epithelial cells, termed 'epithelitis' (Figure 1). Furthermore, these food emulsifiers trigger various cellular processes, including tissue damage, alterations in cell signalling and communication, and induce inflammation even at doses significantly lower (10–20 times) than currently authorized levels. P20 notably interacts with the ferroptosis pathway, a regulated cell death mechanism, influencing immune response and energy production. P80 affects lipid metabolism, the aryl hydrocarbon receptor pathway (involved in environmental toxin detection and response), cellular aging, and immune responses. In a recent double-blind controlled human study, an observed rise in chronic inflammatory diseases was attributed to alterations in the gut microbiota and metabolome.

In conclusion, the intricate relationship between dietary and lifestyle choices, the use of food additives in processed foods, and the subsequent impact on the gut microbiota and epithelial barrier integrity underscores the importance of understanding and addressing these factors in combating the rising prevalence of chronic inflammatory diseases.

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Section C

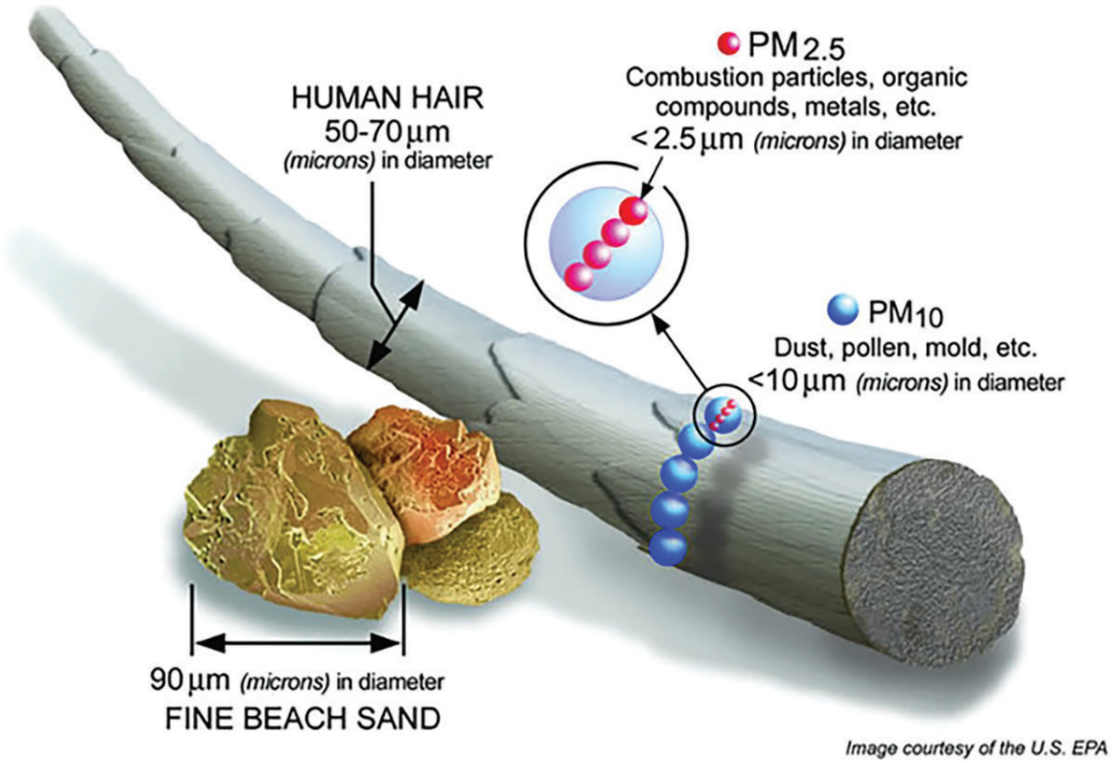

Image courtesy of the U.S. EPA

THE HEALTH IMPACT

* Respiratory allergy and climate change
* Atopic dermatitis
* Allergic diseases in animals

1 RESPIRATORY ALLERGY AND CLIMATE CHANGE

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KEY MESSAGES

- Global warming and climate change events increase the incidence and severity of respiratory allergies by several pathways:
  1. changing pollen characteristics: longer pollen season, increased allergenicity of pollen, change in pollen areal
  2. increased incidence of wildfires and sand and dust (sodiumdoceylsulphate) storms
  3. increasing the concentration and toxicity of outdoor air pollutants such as PM and GHGs
  4. accelerating loss of biodiversity
  5. changing the nutritional properties of foods consumed
  6. decreasing the resilient tolerogenic response due to impaired epithelial barrier and microbiome, impaired diet and loss of regulatory immune mechanisms

Respiratory allergies – asthma, allergic rhinitis and chronic rhinosinusitis are caused by a dysregulation of the immune system in the context of inappropriate resilient response to environmental stressors leading to a dysfunctional epithelial barrier and dysbiosis. They are the most frequent chronic disease worldwide, with a significant economic and societal burden.

During the Anthropocene we witnessed an epidemic increase in allergic diseases, in conjunction with other environmental-driven chronic diseases such as autoimmune, metabolic and neoplastic diseases. Children, pregnant women, the elderly, those with pre-existing chronic diseases or those socio economically disadvantaged are most vulnerable to the Anthropocene aggression.

As the respiratory epithelial barrier is a prime target for environmental aggressors, further increases in the prevalence and severity of respiratory allergies are expected due to the increases in greenhouse gases (GHGs), global temperatures, and natural and anthropogenic pollutants (e.g., particulate matter (PM), carbon dioxide, oxides of nitrogen (NOx), sulphur dioxide, pesticides, microplastics, volatile organic compounds), a consequence of extensive industrialization, modern agricultural practices, and use of fossil fuels for transportation and energy production. Climate change and global warming with accompanying heat and cold stress, wildfires, sand and dust storms, change in pollen characteristics (geographical distribution, concentration, season length, and allergenicity) have all been linked to respiratory disease exacerbations.

Climate change can negatively affect respiratory health directly through increased temperature and humidity and indirectly through extreme weather events, increases in allergens and air pollutants, wildfires, dust storms, and infectious agent transmission. Globally, heatwaves and extreme heat are linked to increased cardiopulmonary mortality. Increased temperature is associated with asthma exacerbations. The impact of increased humidity is less studied, but evidence supports an increased risk of asthma morbidity. Heat accelerates the atmospheric photochemical reaction and increases ambient ozone levels, and may lead to wildfires that produce

extensive amounts of $PM_{2.5}$. Short-term exposure to $PM_{2.5}$ and ozone increase the risk of asthma-related hospital admissions and emergency department visits. The United States Environmental Protection Agency (EPA) identifies ozone and $PM_{2.5}$ as causing or potentially causing new-onset and/or exacerbations of asthma and increased susceptibility to respiratory infections with heightened respiratory mortality risk. Through exposures to storm damage, mold, and infectious disease dissemination in flood water, hurricanes can lead to upper and lower respiratory tract symptoms and new-onset asthma. Aside from directly contributing to disease onset or severity, environmental stress from climate change may impair cardiopulmonary performance during outdoor sports/recreation. Breathing hot and humid air during exercise induces cough and bronchospasm in people with asthma.

Socio-economically disadvantaged groups such as immigrants with limited language proficiency, communities of colour, indigenous groups, or outdoor workers on daily wages face the brunt of climate change because of poor housing infrastructure, proximity to highly polluted areas or flood zones, increased exposure to heat or air pollutants, or poor access to medical care.

Exposures linked to climate change activate complex cellular and molecular processes that affect both inflammatory pathways and immune tolerance. Many climate change events trigger the activation of cellular and molecular pathways at the cutaneous and mucosal barriers of the body.

Biodiversity refers to the variety of life on Earth, from genes to ecosystems, including plants, animals, bacteria, and fungi. While Earth's biodiversity is so rich that many species have yet to be discovered, many species are being threatened with extinction due to pollution, climate change, and population growth with unsustainable resource use. Many basic human needs, such as food, fuel, shelter, and medicine, depend on biodiversity. Climate change surpassed habitat loss as the biggest threat to life on land, with the loss of biodiversity impacting human health in various ways, from zoonotic infections to impaired resilient response. In 2011, von Hertzen et al. proposed that loss of biodiversity also leads to immune system dysfunction and increases the risk of chronic inflammatory diseases, including asthma and allergies, chronic obstructive pulmonary disease, type 1 diabetes, obesity, and inflammatory bowel diseases, and could therefore have important public health implications.

Plants and animals are equally impacted by heat stress and cold spells, by severe weather events and the impaired quality of water, soil and air, with significant changes in their nutritional properties. These changes support the concept of One Health and Planetary Health as holistic approach to the tackle the deleterious impact of climate change on respiratory diseases. Respiratory allergies are proto-types of One Health diseases, as they are directly and indirectly influenced by the health status of the environment (water, soil, and air), plants, and companion and wild animals.

The One Health medical professional connects traditional healthcare with a holistic approach to improving diet, physical exercise/mobility of citizens, housing and working environment, and connectivity with nature. Allergy and asthma specialists can play a vital role in education, communication, and advocacy on climate change mitigation and adaptation measures. For example, climate change was emphasized during the recent Finnish Allergy Program 2008–2018. In the City of Lahti, the EU Green Capital 2021, Natural Step to Health—a Regional Health and Environment Programme 2022–2032—is using respiratory allergies as one of the main focus areas. The goals also include the mitigation of climate change and biodiversity loss.

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2 ATOPIC DERMATITIS

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KEY MESSAGES

- Atopic dermatitis is a complex chronic inflammatory skin disease that is greatly influenced by genetic, immune, and environmental factors
- Environmental influences, such as ultraviolet (UV) radiation, pollution, toxins, allergens, and extreme weather, can directly interfere with the protective cutaneous barrier and skin microbiome, contributing to an individual's overall burden of atopic dermatitis
- The worldwide prevalence of atopic dermatitis has steadily risen over the last thirty years, coinciding with notable impacts of climate change
- Direct results of climate change, including global warming, wildfires, and toxic pollution can directly stimulate cutaneous inflammation, worsening atopic dermatitis in many patients
- Although efforts to mitigate the effects of climate change are underway, true change requires a whole-of-society approach to limiting global warming
- Until drastic improvements in planetary health are seen, we may continue to see increasing numbers and severity of atopic dermatitis cases worldwide

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, characterized by eczematous lesions and pruritus typically affecting flexural surfaces and exposed skin in both adults and children (Figure 1, 2). Caused by skin barrier defects, AD arises from the interplay of genetic, immune, and environmental factors. Affected individuals are especially vulnerable to climate related factors and contact and airborne allergens and irritants from pollution disrupting their already weakened skin barrier and microbiome, as illustrated in the photos showing AD lesions on areas of thinner skin exposed to the environment (e.g. eyelids and dorsal hands).

The worldwide prevalence of AD has steadily risen over the last thirty years alongside worsening climate change, with many factors suggesting a causal relationship. Rises in sea levels and average global temperature as observed by NASA, and associated weather-related disasters (e.g. heatwaves, wildfires, and flooding) have worsened multiple skin conditions and caused unseasonable spikes in weather and pollution-sensitive conditions such as AD.

Increased temperature due to global warming, heat waves, and wildfires, can stimulate proinflammatory cytokine production, inducing pruritus through the thermally-activated transient receptor potential cation channel subfamily V (TRPV) 1, 3, and 4. Furthermore, elevated temperature can promote increased pollen production and distribution, exacerbating allergen-driven skin inflammation and subsequent AD flares through the T-helper (Th) cell 2 signaling pathway in sensitized patients.

Meanwhile, decreased humidity can weaken the skin's barrier function, increasing vulnerability to mechanical stress and potential irritants and allergens. Toxic air pollutants, including volatile organic compounds (VOC) from

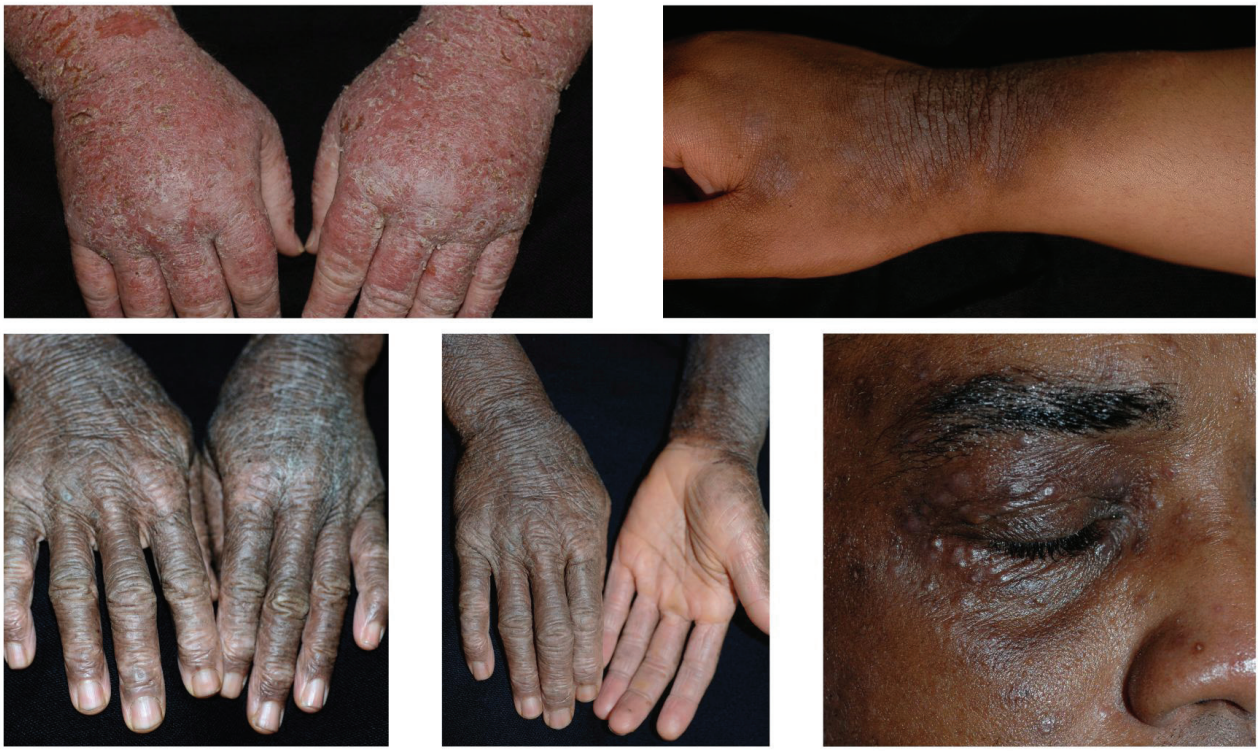

Figure 1 Examples of the clinical presentations of atopic dermatitis (AD). These photos depict areas of the body particularly susceptible to environmental triggers of AD, as they typically remain exposed despite protective clothing and a mask. Of these areas, eyelid skin, which is the thinnest skin on the body, is prone to exacerbations from airborne pollutants causing worsening of AD. (The authors would like to acknowledge Dr. Richard Johnson from Massachusetts General Hospital for permission to use the clinical pictures from his online database.)

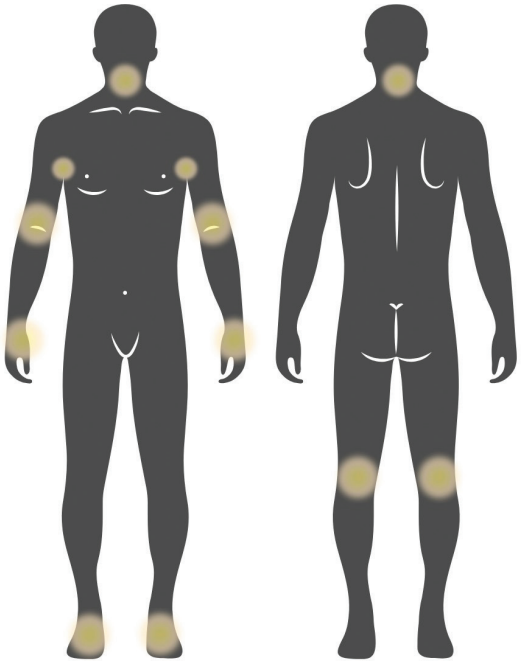

Figure 2 Typical pattern of distribution of atopic dermatitis in children and adults.

traffic-related air pollution and cigarette smoke, as well as particulate matter (PM) from wildfires, can disrupt the skin barrier via increasing oxidative stress and promoting proinflammatory signaling cascades, which interfere with cutaneous microflora, inducing dysbiosis. When coated with lipophilic polycyclic aromatic hydrocarbons, PM can penetrate the skin and activate inflammatory signaling receptors such as the pregnane X and aryl hydrocarbon receptors, leading to a downstream Th2 immune mediated response. Such harmful effects are additive when UV radiation exposure is also involved.

While some efforts toward climate change mitigation are underway, including reductions in fossil fuel emission, promotion of use of renewable energy sources, and adoption of regenerative agricultural practices; real and effective change requires a whole-of-society approach to limiting global warming, and until drastic improvements in planetary health are seen, we may continue to see increasing incidence and severity of AD cases worldwide.

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3 ALLERGIC DISEASES IN ANIMALS

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KEY MESSAGES

- Hypersensitivity disorders, particularly allergy is frequent in animals and affect all commonly treated species
- The main target organs are the skin and the intestinal tract even though a counterpart of asthma is recognized in cats and horses
- Atopic dermatitis, the most frequent allergy in dogs and cats, affect up to 50% of individuals in some predisposed breeds
- Treatment of allergic disorders in animals is mainly based on allergen avoidance, use of immunomodulatory drugs and allergen-specific immunotherapy
- The recent launch of a Mab against the pruritogen cytokine IL-31 has dramatically contributed to the improvement of the quality of life of affected dogs

Hypersensitivity disorders represent a major burden for companion and large animals, especially dogs, cats and horses. The other species are probably also affected even though data are only sparse. Major allergens include insect (flea, flies), environmental (house dust and storage mites, pollens, molds, epithelia) and food allergens. From a clinical point of view, the skin and the gastrointestinal tract are by far the most frequently affected, even though horses and cats may present with clinical signs of allergic asthma. Insect allergies were the first well characterized allergy disorders in animals and are considered to be type I and type IV hypersensitivity reactions. In dogs and cats, fleas are frequently involved and flea hypersensitivity dermatitis was long considered the first cause of skin disorders in both dogs and cats. In horses, numerous flies have been suspected to induce similar disorders. Affected animals present with intense itch usually localized on the dorsal aspect of the body. In contrast, bee and wasp allergies are comparatively rare in domestic animals and are usually associated with urticaria, angioedema and/or anaphylaxis. In fact, it has been shown that one third of the dogs are sensitized to insect venoms but only a few of them developed clinical signs.

Environmental allergies mostly target the skin in animals. Atopic dermatitis is the most frequent diseases in dogs and in some breeds (French Bulldog, Shar pei, West-Highland-White Terrier more than 50% of individuals are affected. Affected animals present with itch and erythema usually localized to the head, feet and ventral parts of the body (Figure 1). Canine atopic dermatitis is considered the counterpart of human disease and most of the findings observed in humans are applicable to the dog. In fact, canine atopic dermatitis is a Th2 driven disorder in the acute phase of the disease and is mainly Th1 in the more chronic one. The most frequently involved allergens are house dust mites even though similar symptoms have been observed with pollen and food allergies. AD is less well characterized in cats, horses and other domestic animals but the disease is recognized in all of these species. Mites and pollen allergens are also involved in the pathogenesis of equine and feline asthma. Equine heaves is a spontaneous occurring asthma-like condition

affecting 10–20% of adult horses in the northern hemisphere and other temperate climates. Similarly to asthma, heaves is a chronic disorder of the airways, which is characterized by variable and recurring airflow obstruction, bronchial hyperresponsiveness and airway inflammation. During disease exacerbation, horses present increased respiratory efforts at rest, coughing and exercise intolerance. Clinical signs are triggered or exacerbated by inhalation of dust particles present in the stables, especially those associated with hay feeding. Neutrophils and macrophages are present in large numbers in the airways of horses with heaves and may contribute to the disease through the release of several inflammatory mediators. Experimental models of feline asthma have been developed with cats sensitized to various allergens including mites and pollens. Similarities of horse heaves with the human asthma are currently being used to evaluate airway remodelling and its reversibility in ways that are not possible in humans for ethical reasons. Research perspectives that can be relevant to asthma include the role of neutrophils in airway inflammation and their response to corticosteroids, systemic response to pulmonary inflammation, and maintaining athletic capacities with early intervention.

Food allergies are also frequent in pets and may affect the skin the gut or both organs. The diagnosis is complicated by the absence of reliable laboratory or skin tests. For this reason, elimination diet followed by rechallenging is still considered the gold standard.

The diagnosis of other hypersensitivities in animals is based on skin testing and/or serum IgE testings. Both tests are considered reliable even though sensitization without any clinical signs is frequent. Cross-reactive carbohydrate determinants are also frequently associated with false positive tests, especially with pollens.

Treatment of allergic disorders in animals is mainly based on allergen avoidance (insects: use of antiparasitic treatment avoidance or organic dust for heaves), use of allergen-specific immunomodulatory (AIT) drugs such as glucocorticoids, Jak inhibitors such as oclacitinib or cyclosporine and desensitization. AIT is mainly used for the treatment of atopic dermatitis in dogs and cats and is successful in about 60-70% of the cases. Bronchodilators and corticosteroids are administered systemically or by inhalation in heaves to provide rapid relief of airway obstruction, or when control of the environment is partial or absent. When itch is the main clinical signs in dogs, IL-31 monoclonal antibodies (Lokivetmab) are used and are associated with a rapid and long-lasting relief.

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Section D

PREVENTION, ADAPTATION AND MITIGATION

* Mechanism and biomarkers for prediction, prevention, follow up and outcomes
* Protection from extreme weather events
* Sustainability in health care and research
* Nature-based solutions to counteract non-communicable diseases
* Confronting biodiversity loss in endangered animal species
* Education for achieving planetary health
* Epithelial barrier theory and suggestions to patients
* The role and responsibility of scientific organizations
* Patient advocacy
* The role and responsibility of patient organisations
* Planetary health requires integrated approaches for flourishing at all scales

1 MECHANISM AND BIOMARKERS FOR PREDICTION, PREVENTION, FOLLOW UP AND OUTCOMES

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KEY MESSAGES

- Impaired diet, microbial dysbiosis, increased urbanisation and modern lifestyle and epithelial barrier damage act in synergy to break the immune tolerance and fuel chronic local and systemic inflammation
- Understanding the interaction between the environmental aggressors and the resilient adaptive response requires the exposomic and the One Health approach
- NCDs' management should incorporate the evaluation of climate-change driven changes in exposure and measures tailored to the individual needs and to the environment
- Heath equity should be at the center of mitigation and adaptation strategies

While there is ample epidemiological evidence associating climate change with allergies and asthma, and with other non-communicable chronic diseases (NCDs), the climatic factors mediating these changes and the mechanisms underlying these associations need further study.

Impaired diet, increased urbanisation and modern lifestyle (hygiene, antibiotics, "old friends" and biodiversity hypotheses), increased time spent indoor and less contact with nature, less physical activity, exposure to toxic chemicals in air, water, foods, and to newly introduced chemicals from detergents and disinfectants, shampoos and toothpaste, have been put forward to explain the underlying mechanism mediating the sharp increase in the chronic inflammatory diseases (allergic, autoimmune, metabolic, neoplasia).

Environmental exposures activate complex cellular and molecular processes at the cutaneous and mucosal barriers of the body that affect both inflammatory pathways and immune tolerance. Activation of epithelial cells through danger receptors triggers the production of TSLP, IL-33 and IL-25 and inflammasome-related interleukins, overproduction of pro-inflammatory mediators including prostanoids, and leukotrienes, generate oxidative stress, DNA modifications and increased permeability of the barrier. This leads to the perpetuation and amplification of chronic local and systemic inflammation. These events operate in a synergistic fashion at all barrier sites (skin, airways, gut). Some of the above-described effects lead to only mild or smoldering inflammation. However, these effects can not be underestimated since persistence for a long time can cause irreversible organ dysfunction due to tissue damage and/or fibrogenesis. Living cells can mitigate environmental stressors through adaptive mechanisms (allostasis). The level of resilience is key to maintaining health by keeping the balance between the impact and response. Allostasis starts during early-life immune maturation, with efficient regulation of the resilient response requiring the diet, microbiome, and the epithelial barrier as key pillars ensuring that the immune system adapts to challenges by establishing, maintaining, and regulating a tolerogenic adaptive response. Many questions yet remain to be solved (Table 1).

Studying the complex interaction between environmental aggressors and the resilient adaptive re-

TABLE 1

Unmet needs in understanding the mechanisms of environmental-driven chronic diseases
How the allostatic load is continuously shaped by the multiple concomitant environmental stressors
What is the role of the immune system, microbiota, epithelial barrier and diet in promoting resilience
What is the population of interest ("the model"), what is the nature (duration, frequency, timing) and magnitude (concentration and dose) of relevant exposures, which associations are relevant for a particular NCD
What are the mechanisms driving the environmental endotypes versus the genetic background
What is the value of population level interventions versus the personalised medicine approach

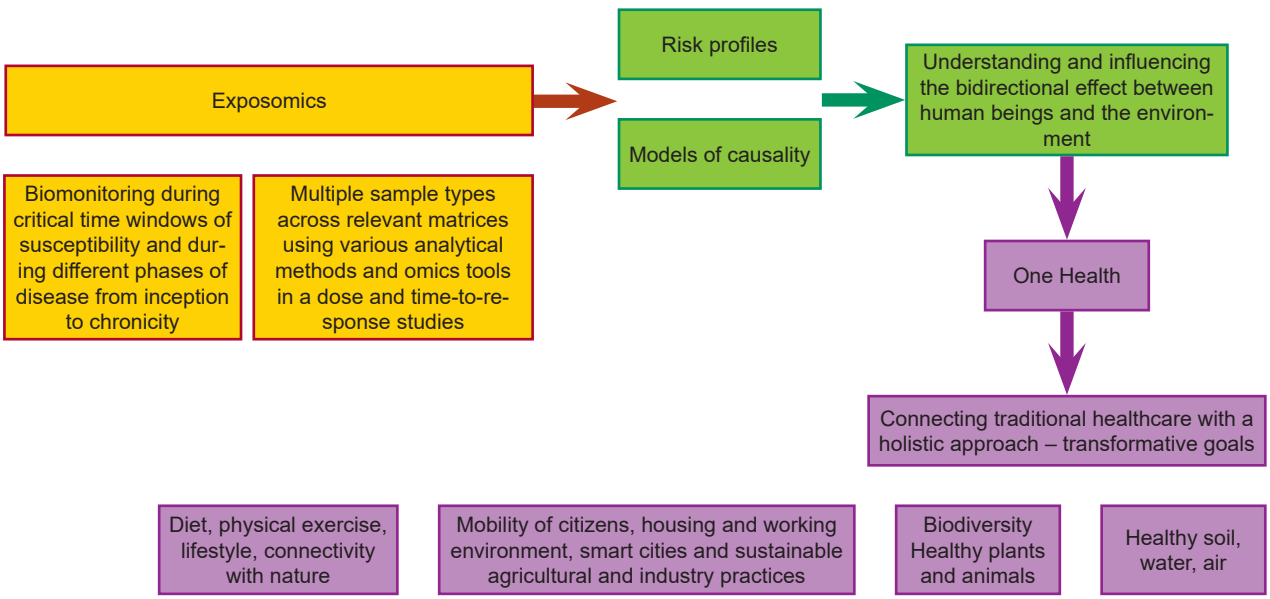

Figure 1 Tackling the complex interaction between environmental aggressors and the resilient adaptive responses.

sponses requires the exposomic and the One Health approaches (Figure 1).

By providing risk profiles and models of causality, the exposomic approach is the best tool helping to understand and influence the bidirectional effect between human beings and the environment. The ability to characterize environmental exposures through biomonitoring is key to exposome research efforts. Both traditional and nontraditional biomonitoring methods should be used. The ideal exposure measurement evaluates multiple sample types (biological, questionnaires, etc.) across relevant matrices using various analytical methods and integrates -omic tools in a dose and time-to-response studies using experimental model systems to gain detailed mechanistic information. Biomonitoring during critical time windows of susceptibility and during different phases of disease from inception to chronicity also has the potential to validate new tools for risk assessment and to estimate the burden of environmental disease. Numerous biomarkers of environmental exposures have been identified that may quantify or predict the individual risk of disease. These biomarkers can be classified as biomarkers of exposure, intermediate biomarkers of early effect (biomarkers of susceptibility), or biomarkers of response/disease. Furthermore, biomarkers of exposure can be grouped according to the environmental stressor.

The One Health concept states that human health is largely dependent on environmental health (air, water, food and soil quality) intermingled with plant and animal health. As a collaborative and interdisciplinary strategy One Health connects traditional healthcare with a holistic approach improving diet, physical exercise/mobility of citizens, housing and working environment, and connectivity with nature and thus best support the advanced management of complex, multifactorial diseases driven by a maladaptive resilience response to the exposome.

Given the important role of climate change in driving NCDs, their management should be personalized to address climate change-driven changes in exposure and ideally incorporate modifications tailored to individuals' needs and the environment. We need a coordinated approach that synergizes efforts across sectors including public health, veterinary medicine, environmental science, and community engagement. These efforts should be coupled with the advantages offered by the exposomic approach, with health equity at the center of all mitigation and adaptation strategies and with the integration of transformative goals into local governance.

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2

PROTECTION FROM EXTREME WEATHER EVENTS

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KEY MESSAGES

- Climate change is causing a range of impacts on plants and the pollen they produce
- The resulting increases in exposure to aeroallergens are causing increases in allergic sensitisation and allergic respiratory diseases such as hay fever and asthma
- Rapid-onset extreme weather events such as thunderstorm asthma may also be affected
- The most important adaptive action to protect against these increasing threats is monitoring of aeroallergens such as pollen and fungal spores
- Worldwide cooperation is required to rectify a serious global inequity in the coverage of such monitoring, with government responsibility and United Nations involvement
- The development of pollen forecasting, transition from manual to automated real-time pollen monitoring, and the utilisation of communication technologies such as smartphone apps are other important advances that will protect

This chapter briefly explores climate change - one of the greatest planetary health challenges facing humanity. In particular it describes the impacts of climate change on aeroallergens and extreme weather events and the implications of these for allergic respiratory diseases. It then outlines several adaptive actions that will provide some level of protection against these increasing threats.

Both the increasing atmospheric carbon dioxide concentration due to the burning of fossil fuels, and the resulting rapid and substantial increases in global temperatures, are causing a range of impacts on plants and the pollen they produce. The start, end, and duration of the pollen season of various plants is changing, in many cases starting earlier and going for longer than in the past. Some plants are also producing more pollen, and in at least one key allergenic species (ragweed), the pollen is becoming more allergenic.

These long-term increases in exposure to aeroallergens are causing increases in allergic sensitisation and allergic respiratory diseases such as hay fever and asthma (Figure 1).

Rapid-onset extreme events may also be affected. For example, the world's largest, most catastrophic epidemic thunderstorm asthma event took place in Melbourne, Australia, in November 2016. The interaction of thunderstorms and extremely high levels of grass pollen (produced by record rainfalls and high pastureland growth) resulted in extraordinarily high acute exposure which caused thousands of excess respiratory-related emergency department presentations, hundreds of excess asthma hospital admissions, and 10 deaths.

The most important adaptive action to protect against these increasing threats is monitoring of aeroallergens such as pollen and fungal spores. While some parts of the world, such as Europe, are well served with such monitoring, in other parts of the world the monitoring is spare or there is none, such as for large parts of Africa, Asia, and South America (Figure 2). This is a serious global inequity that requires worldwide cooperation to rectify. National governments need to take

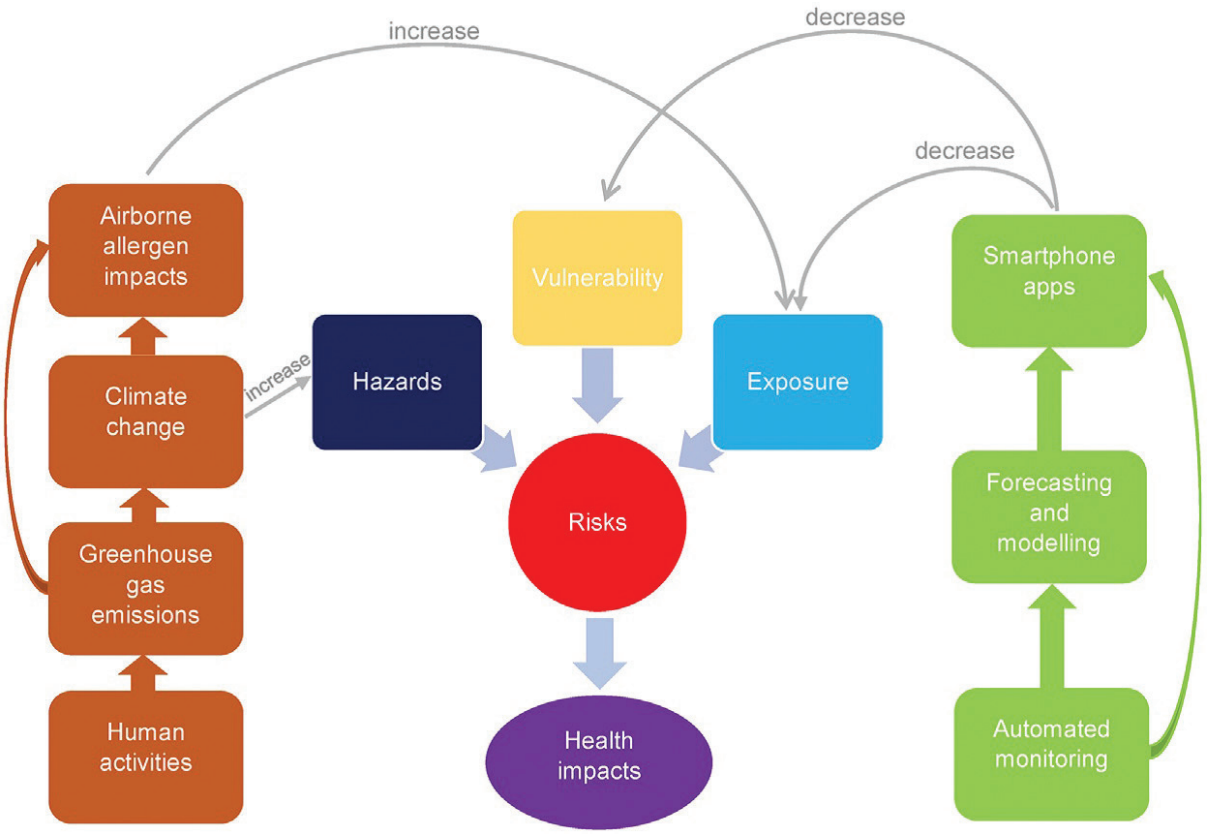

Figure 1 Impacts of climate change on airborne allergens (brown), the consequent impacts on human health, and three connected adaptation approaches (green) that can prevent or reduce health impacts by decreasing exposure and vulnerability. *(Beggs et al. 2023; copied and redistributed (figure unchanged and figure caption modified) under the CC BY-NC-ND license https://creativecommons.org/licenses/by-nc-nd/4.0/)*

responsibility for this monitoring, ensuring that it is sustainable, standardised, and suitable for the local context. Further, the framework for essential international cooperation should be provided by the United Nations, as it does for weather, climate, and water through the World Meteorological Organization.

Pollen monitoring provides the data for the development of pollen forecasting and warning systems which empower people to manage their disease (Figure 1), as is now the case in Melbourne with the world's first routine daily thunderstorm asthma forecast. The transition from manual to automated real-time pollen monitoring, and the utilisation of communication technologies such as smartphone apps are other important advances that will protect.

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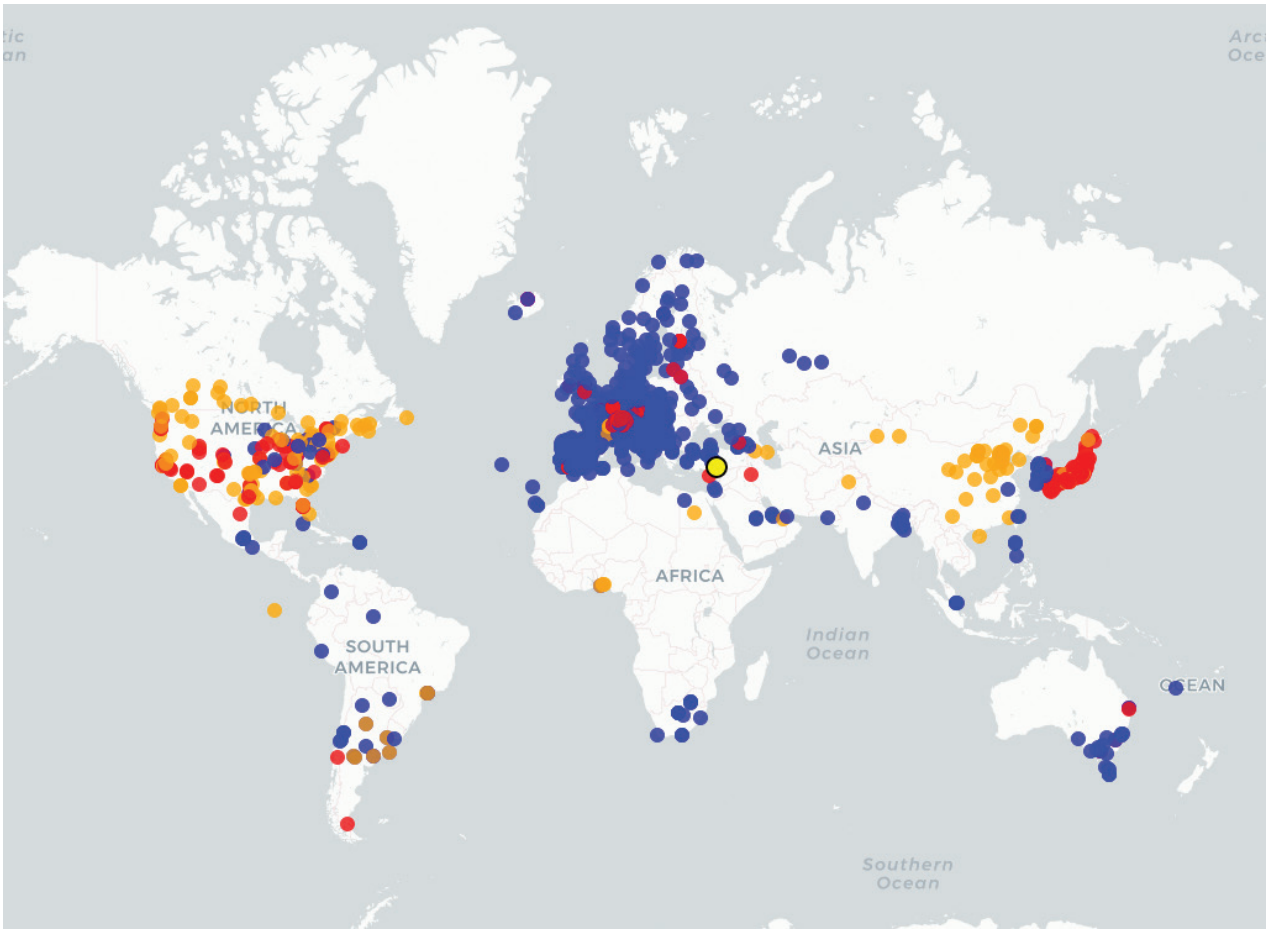

Figure 2 Global map of pollen monitoring stations. Blue dots: Hirst (Lanzoni/Burkard) manual monitoring system; yellow dots: other manual systems; red dots: automatic monitoring systems. (*https://hub.eaaci.org/patients_resources/worldwide-pollen-map/)*

3 SUSTAINABILITY IN HEALTH CARE AND RESEARCH

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Inês Paciência
University of Oulu Oulu, Finland

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KEY MESSAGES

- Health care and research for human and veterinary patients cause an immense, unintended, negative environmental impact
- Counteractions can be made on the individual or the institutional level, up to influence on politics and legislative
- Recommendations comprise i) rethinking of routine procedures in health care (e.g. waste management, favour reusables), ii) careful planning of studies and experiments (e.g. material orders and use, change of clothes/gloves), iii) as well as meeting culture (prioritize telemedicine, tele conferences, hybrid congresses)

From hospitals to pharmacies and research laboratories, from allied health professionals to physicians in clinicals and researchers at the bench: Health care and research aim at maintaining, optimizing and improving the health status of human and veterinary patients as well as the environment. Paradoxically, the way this is done at the moment causes an immense, unintended, negative environmental impact.

Global greenhouse gas emissions (GHGE) from the health sector range on place 5 with 4.4% of total GHGE, and a huge overall environmental impact between 1-5% of the total global impact (and more than 5% for some national impacts) depending on the indicator considered. For research, estimates range from 5.6 to 9.6 tons for chemistry and from 4 to 15 tons for life sciences/researcher/year, all on top of private-life emissions. Major sources are travel by plane, use of electricity and computing. In summary, researchers' activities emit 2–5 times as much as an average European citizen (reviewed by Freese et al.).

Both sectors, health care system and research, consume a lot of resources like plastic, water and energy, and produce a huge amount of waste, like plastics, drug-leftovers or hazardous chemicals. Apart from direct applications for patients or research studies, also the indirect impacts need to be considered: a) mobility of staff and patients/animal holders; b) food and feed (type and waste) for patients and staff; and c) travelling to congresses. In their comprehensive review and case-study including personal data on travelling and waste production at the University of Groningen, Freese et al. impressively show the impact of research on several levels (Figure 1). Importantly, input for improvement, and guidance on practical steps are readily available (Table 1).

Counteractions in the health care system (Figure 2) can be made on the individual level, on the directive management level up to political and legislative regulations (Table 2). Measures can simply apply to procedures, like (i) avoiding food waste by integrating the hospitalized patient in food choice (type, amount, adjusted to medical condition); (ii) planning lab experiments carefully so that frequent change of one-time equipment is unnecessary (e.g., removing gloves for phone calls, frequently changing overshoes when leaving and returning to cell-culture room). Sometimes it is just a change to an alternative that is already highly effective, like providing a **sustainable diet** to patients and staff (75% plant-based, seasonal, regional, fresh food); types of **asthma inhalers** (from pressurised metered dose inhalers (pMDI) to a dry powder

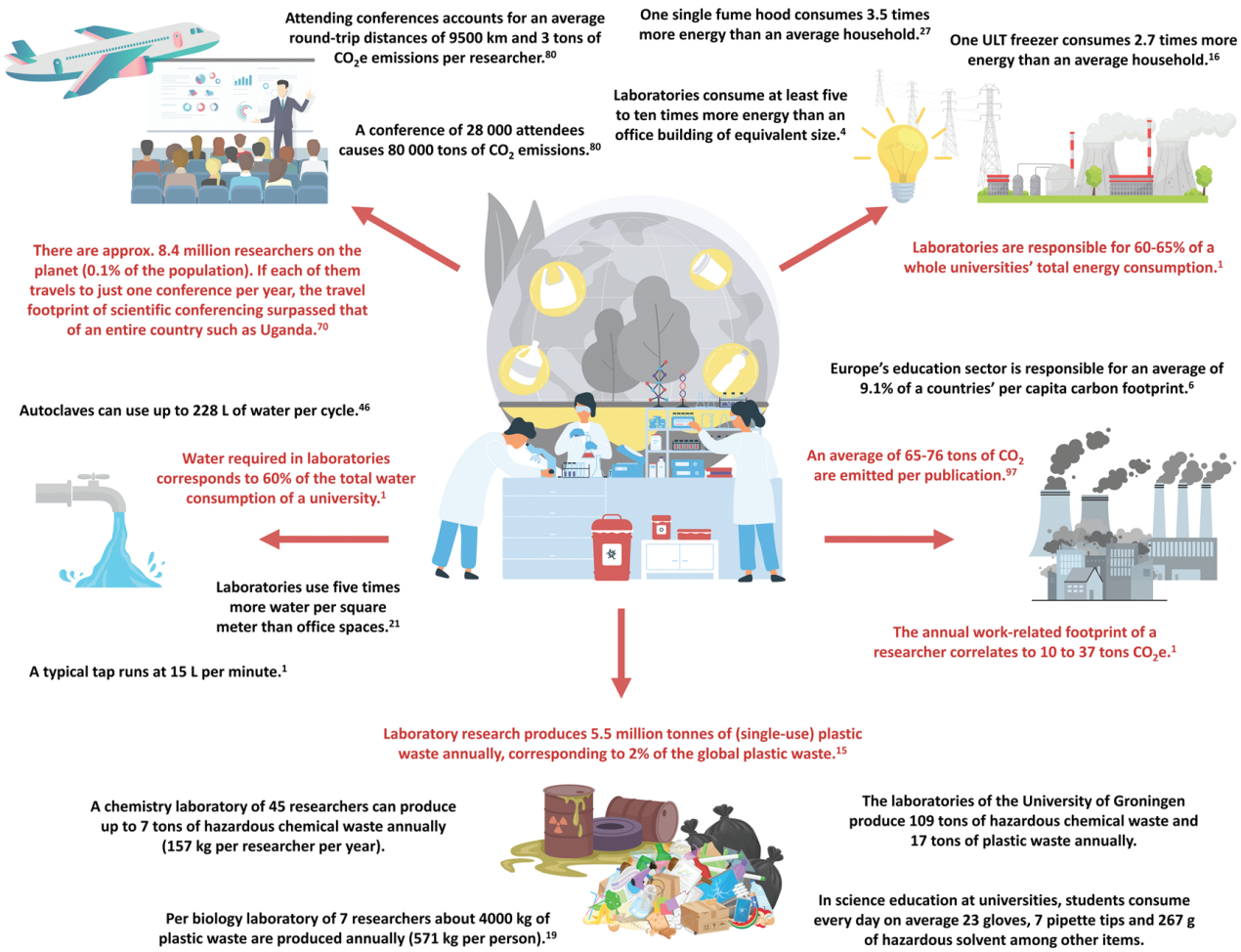

Figure 1 Environmental impacts of science, research, laboratories reach from production of plastic waste and hazardous waste to travel mode emissions as well as energy and water consumption. *(Unmodified from open access article by Freese et al.3 under a Creative Commons Attribution 3.0 Unported Licence, CC by 3.0)*

inhaler (DPI)); anaesthetic gases; type of congress attendance (onsite vs. online); or the type of mobility for staff and patients travel (using sustainable public transport like subway, tram and train instead of cars and plane). More investments may be needed for a switch to **telemedicine** regarding technical equipment and software, time management or patient education. Importantly, big data transfer and storage need to be omitted to not outweigh the beneficial effects.

In laboratories uncomplicated practices can make a significant impact (Table 1): switching to re-usable devices and containers (e.g., glass pipettes, spatulas, containers; refillable pipette tip boxes); re-sizing (use smallest plastic vial that fits respective volume); re-thinking (which step is needed) and re-cycling (companies that have a take-back culture; clean plastic separation in respective country for industrial recycling). Energy saving in labs can be achieved by turning off lights and devices that are not in use instead of stand-by mode (water bath, computer screens, centrifuge); by organizing ultra-deep freezers carefully (sample list outside; no unnecessary samples or cardboard boxes stored; short opening times); or switching to new technology that can save up to 40% of electricity usage.

In summary, changes on an individual or institutional level can already have huge beneficial effects in sustainability of health care and research. When further political/legislative/infrastructural support is needed, it could and should be initiated bottom-up even from individual people or teams.

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TABLE 1

Sustainable laboratory measures based on impact *	
Research and education	• Enhance reproducibility by conducting research at the highest quality possible, saving resources and time. • Provide detailed information on reaction conditions, procedures, and data to enhance reproducibility. • Record and share negative results to avoid unnecessary reproduction attempts. • Educate students and new lab members on sustainable laboratory and research practices.
Travel and conferencing	• Avoid air travel as much as possible and prioritize travel by train. • Prioritize local conferences accessible by train. • Attend meetings and conferences online rather than in person. • Attend only the most important conferences overseas via air travel. • Use resources on journey planning, which is discouraging traveling by airplanes. • Unavoidable sights should be offset with verified carbon standard projects supporting jet fuel research.
Energy efficiency	• Prioritize variable air volume (VAV) fume hoods over constant volume (CV) air supply systems. • Closing the sashes of fume hoods reduces its energy consumption between 40 and 67%, in addition to being safer. • Equipping fume hoods with sensors that trigger automatic sash closing facilitates this action. • Increase the temperature of a ULT freezer from −80 °C to −70 °C to reduce energy consumption by 30–40% as sample stability and recovery are not affected. • Maintain an inventory list, share freezer space, and organize regular freezer cleanings to remove unneeded samples, frost buildup and dust accumulation. https://www.freezerchallenge.org. • Turn off equipment, when not in use. Devices should be turned-off by default and only be switched on, when needed. Here multiplugs, timers and switches can facilitate a behavioural change, while stickers can serve as reminders. • Utilize and run equipment such as autoclaves, ovens, and dishwashers only when full. • Replace overhead lights with LED bulbs.
Data centres and computations	• Prioritize digital, paperless options such as digital laboratory journals and online clouds and minimize printing. • Run calculations at times and locations with the highest amount of green energy. • If privacy allows, prioritize data centres in locations with greater sustainable source of electricity to minimize carbon footprint. • Evaluate the set point temperature in server rooms to reduce active cooling. • Calculate the carbon footprint of the research and include those in cost-benefit analyses. • Improve the efficiency of code, prioritize C++, and optimize hardware.
Water	• Retrofit/update autoclaves with systems that recirculate or reduce water consumption, which can save about 32 000 L of water per week. • Implement aerators on taps. • Utilization of waterless condensers. • Cooling devices and systems should only operate in closed loops and rely on recirculated water.
Chemicals	• Avoid the generation of surplus quantities. • Implement an online chemical search and location system (so called inventory) and regularly maintain its content. Make sure that chemicals are findable and accessible. • Share chemicals with other labs/group-members and consult the chemical search system if the compound needed is already available before ordering a new one. • Conduct reactions in the smallest volumes possible (i.e., rightsizing experiments) and check for their success before upscaling. • Minimize the number of physical experiments via computational modelling and simulations, where applicable. • Utilize efficient robotic, automation, and artificial intelligence (AI) tools for high-throughput experiment optimization ('lab of the future'). • Purchase the smallest possible quantities of chemicals sufficient for a given experiment. • Prioritize benign and less hazardous reagents and solvents. • Recycle solvents and chemicals for cleaning.

TABLE 1

continued

(Single-use) consumables	• Reduce, reuse, recycle. • Replace single-use plastics with glassware. • Reuse plastic where possible. • Results are not affected through reusing glass or plastic as no carryovers or contamination is observed. • Reduce shipments and packaging. • Consult suppliers and producers if there is a take back scheme for used consumables. • Try to implement a recycling scheme for plastic consumables such as gloves, pipette tips or plastic tubes if contamination can be excluded.
Glass waste	• If feasible, glassware should undergo repairs; if repair is not possible only then opt for disposal.
Logistics and procurement	• Reduce the number of shipments and packaging by coordinating orders from across the institute/group. • Coordinate orders of commonly used items via 'central stores' within the institute, which store items in bulk and supply demands on site. • Prioritize local and responsible suppliers with a detailed sustainability plan. • Ask manufacturers and suppliers about life cycle assessments, takeback schemes, and more sustainable alternatives to standard products.
Resource efficiency	• Whenever feasible, laboratory equipment should undergo repairs; if repair is not viable, disposal and replacing with new equipment should be considered as the last option. • Reuse equipment, computers, and furniture internally at locations/groups/projects that are in need of specialized equipment. This way group resources are preserved as well as less waste is being produced. • Equipment that is not needed anymore but still intact should be donated or sold via second-hand refurbishing schemes. • Implement SOPs and report every detail of experiments, this way replication and reproducibility is enhanced, and less waste is generated.
Working environment, commuting and finance	• Develop a sustainable travel policy prioritizing low-carbon forms of travel. • Prioritize public transport or biking whenever possible. • Provide a network of cycle paths, bike sheds, and other related facilities. • Offer a free train, metro and bus pass for staff and students. • Provide charging possibilities for electric vehicles. • Provide technical equipment for home office and virtual meetings. • Equip buildings with solar panels to provide renewable energy. • Switch to a sustainable electricity provider (solar, wind power). • Improve the retirement plans of staff, by switching to a sustainable solution and an ethical pension provider. • Move the bank and institution accounts to a financial institute committed to sustainable goals. • Prioritize plant-based (vegetarian and vegan) menu options over meat-based diet and avoid food waste. • Support actions on nature and biodiversity on the campus. • Prioritize https://www.ecosia.org/ as the search engine for internet searches.

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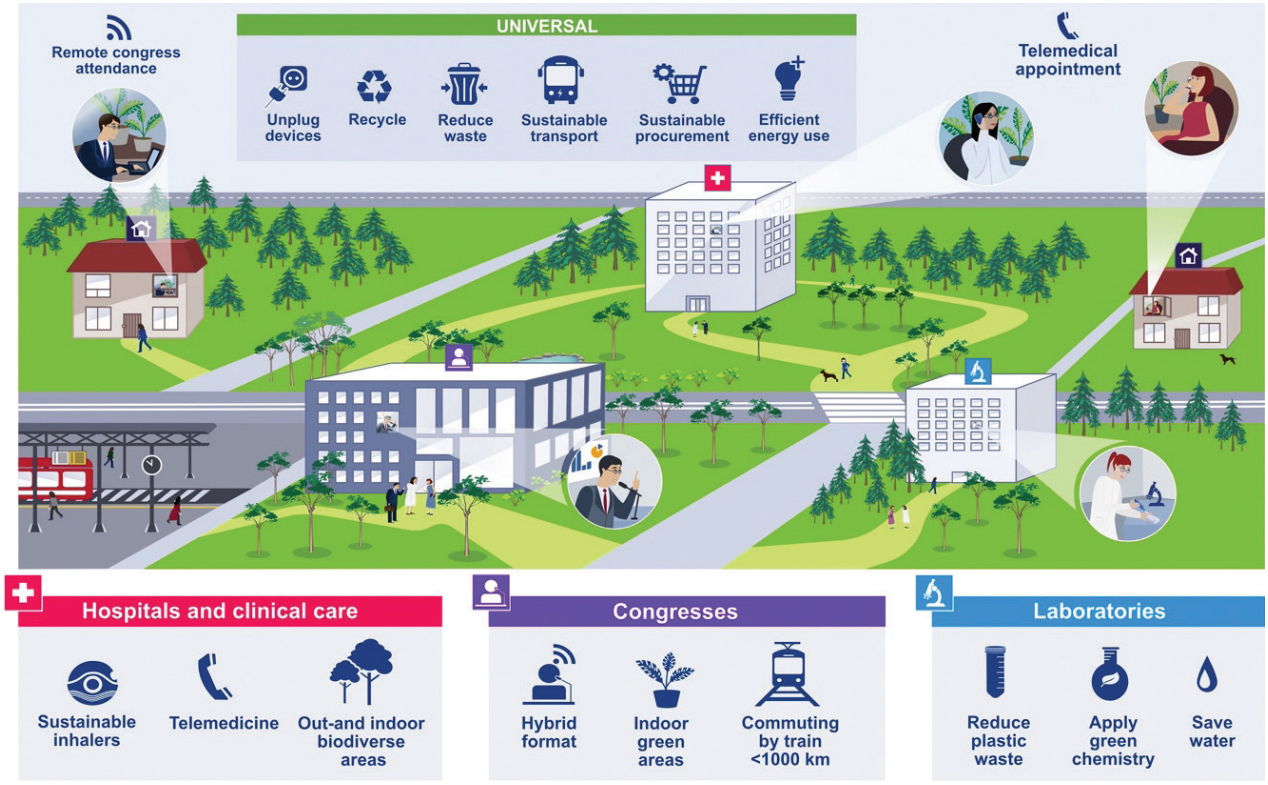

Figure 2 Measures to improve sustainability of health care and research facilities. Systems and procedures can be implemented by individuals as well as on institutional or national levels, and can reach from management of individual devices (like ultra-low freezers, installing green areas) up to reimbursement policy for congress travel expenses (e.g., priority for sustainable mobility). *(Used with kind permission unmodified from the article Pali-Schöll et al.4 published open access under CC BY-NC-ND 4.0.)*

TABLE 2

WHO proposed elements to be included in a national policy for environmental sustainability in health systems *
Overarching aim: to adopt a national environmental sustainability policy for health systems including the following elements:
• to minimize and adequately manage waste and hazardous chemicals
• to promote an effective management of resources
• to promote sustainable procurement
• to reduce emissions of greenhouse gases and air pollutants by the health system
• to prioritize disease prevention, health promotion and public health services
• to engage the health workforce as a mean to reach sustainability
• to increase community resilience and promote local assets
• to create incentives for change
• to promote innovative models of care

** World Health Organization E. Environmentally sustainable health systems: a strategic document. 2017; https://iris.who.int/bitstream/handle/10665/340375/WHO-EURO-2017-2241-41996-57723-eng.pdf?sequence=3. Accessed 11 June, 2024*

4 NATURE-BASED SOLUTIONS TO COUNTERACT NON-COMMUNICABLE DISEASES

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KEY MESSAGES

- Nature-based solutions focus on primary prevention and disease management by increasing contact with natural biodiverse environment
- Exposure to natural environments like green spaces and farms has important health effects on the modulation of the immune system and the development of chronic inflammatory diseases
- In a One Health sense, diverse environments like green spaces and farms are key for healthy plants, livestock animals, and thereby for the health of people and animals

INTRODUCTION

Loss of contact with and closeness to natural environments like green and blue spaces, summarized by Haathela et al. as "nature deficiency" recently, decreases the services provided by ecosystems. Those include regulating air pollution, noise, heat and water, helping with climate change mitigation and adaptation, providing food, medicinal plants and biomass, as well as recreation, landscape aesthetics and social cohesion. Nature-based solutions focus on primary prevention and disease management by increasing contact with natural, highly biodiverse environment, and by building resilience to food and water insecurity. Among these measures is spending time in close contact to greenness or on farms.

LIFE IN GREEN AREAS

On a direct, individual level, measures could compile spending time in forests and green spaces; planting flowers and herbs on the window sill; providing already small children in kindergarten and schools with containers filled with enriched soil (*e.g.*, compost) and encourage them to plant their own seasonal fruits, berries or vegetables; arrange green backyards, facades and indoor walls in buildings from offices to hospitals; eat diverse natural and sustainable food; and support contact with animals and people (Figure 1). Such measures do not only influence mental health of people, but also impact conditions that might support physical health. For example, in office workers with indoor green walls, microbiome diversity with *Lactobacilli spp.* on skin increased within 28 days while simultaneously IL-17 in serum decreased. In addition, daily exposure to enriched sandboxes and backyards was associated with an increase in skin proteobacterial richness, decreased skin *Clostridium sensu stricto*, increased plasma IL-10 and lowered IL-17 in children.

These exposures to natural environments, including neighborhood green and blue spaces, therefore, have several important health effects on the modulation of the immune system and the development of chronic inflammatory diseases, such as asthma and allergic diseases. A longitudinal study including 730 children support the role for both longitudinal, but particularly late-childhood exposure to green spaces in the prevention of allergic sensitization in children. However, greenness has spatio-temporal variation, which depends on the climatic conditions. The season of exposure is particularly important due to increased pollen exposure in green spaces in certain seasons. A recent study suggested that early-life exposure to green spaces

Figure 1 Nature-based interventions. *(All pictures/photographs are courtesy of Isabella Pali-Schöll)*

during spring increases the risk of developing allergic rhinitis in childhood, while during the summer, similar exposure reduces the risk of allergic rhinitis. For allergenicity assessment, an index might help to apply corrective measures to mitigate the impact of pollen emissions at various levels, like planning and design, handling and management, and strengthening of urban green-infrastructure elements.

Several other ecosystem disservices are discussed, *e.g.*, poisoning, emission of biogenic volatile organic compounds, unpleasant smell, increased water consumption, wildfire risk, and management costs. In most cases, the benefits (*i.e.*, indirect costs saved for instance for days taken off from work due to illness) by far outweigh direct costs (*e.g.*, buying and planting trees, service and management of green areas). To increase private and political motivation, education on specific considerations for green spaces is needed, so benefits will finally reimburse invested time, costs, workload and unwarranted effects.

The "*Nature Step*" has been actively endorsed by the Finnish Allergy Program, suggesting the consideration of protective factors associated with a healthy lifestyle and relationship with nature. The program advices to not avoid exposure to environmental allergens unless it has been proved necessary, and to increase contact with the natural environment (*e.g.*, through regular physical exercise, a healthy diet such as a traditional Mediterranean or Baltic diet, and preference for local food).

LIFE ON A FARM

Asthma- and allergy-preventive effects are observed when children grow up on farms and drink raw cow's milk. Several molecules are held responsible for these positive effects. The whey-protein beta-lactoglobulin (BLG) as carrier for beneficial ligands is an important player, present not only in milk, but also in cow stable dust and ambient air, distributed by cattle urine. BLG can be associated with binding partners like zinc, iron-siderophores, or vitamins. In this associated form, BLG mediates immune resilience or modulates the immune response away from allergy and reduces symptoms also in allergic human patients. In the mouse model, stable dust containing BLG was able to prevent allergic symptoms against milk or birch, while BLG-depleted dust was less effective. To provide the necessary binding partners for such carrier molecules, which are present in mammals but also in plants, a healthy and biodiverse soil and environment for food plants and livestock animals is key.

SUMMARY

It is of utmost importance to establish policies to maintain existing green areas, establish new greening and renaturation not only in urban areas but also at the countryside, where sealing of soil is increasing for industry and streets. Diverse environments are key for healthy food plants and presumably also for livestock animals, thereby in a One Health pattern also for the health of people and animals. Biodiverse environment like green spaces and farms and nature-based life-style can positively act on mental as well as on physical health of people and animals.

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5 CONFRONTING BIODIVERSITY LOSS IN ENDANGERED ANIMAL SPECIES

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KEY MESSAGES

- Mobilizing Global Action: The urgent need to safeguard Earth's biodiversity is evident as habitats vanish and species face extinction
- United Action: The entire world must join the forces to believe that this is a real issue requiring an urgent action
- Human Footprint: Our actions, from climate change to habitat destruction, fuel a crisis of species loss and driving us towards a "sixth mass extinction"
- Finding Harmony: As we venture into new realms, it's crucial to strike a balance that cherishes nature and protects all life forms from harm
- Effective Solutions: Combating species extinction demands a diverse toolkit, including cutting-edge technologies and innovative funding strategies

Given the concerning loss of habitats worldwide and the looming threat of extinctions of species and declining populations, urgent initiatives are needed to protect Earth's diverse life forms. While evolution has finely tuned species to their environments over millennia, recent human activities such as climate change, habitat destruction, overexploitation, pollution etc., have left many habitats unable to support their diverse inhabitants. Despite many but limited efforts, humanity has struggled to halt the decline or extinction of species (Figure 1).

The nature of the Earth is rapidly changing due to climate change, habitat degradation, overexploitation of animal populations, and pollution. The Living Planet Index (LPI) and Living Planet Database (LPD) compile data on over 31,821 populations of 5,230 mammal, bird, fish, reptile, and amphibian species. Between 1970 and 2018, 5,230 species experienced a 69% decline in abundance, leading to a 60% average decline in species abundance over the past five decades, according to the LPI (Figure 2). The IUCN Red List reveals over 44,000 species threatened with extinction, 28% of all assessed species, (4008 animal species critically endangered, Table 1) highlighting a "sixth mass extinction" due to human activities, habitat loss, and rapid animal extinctions (Table 2) surpassing historical rates. Additionaly, local breeds, particularly in Europe-Caucasus, and also worldwide face extinction due to choosing animals for breeding based on their ability to produce high quantities of meat or milk to maximize profits, threatening biodiversity and traditional livelihoods.

Technological advancements like GPS following, genetic studies for species differentiation etc. greatly enhance our ability to monitor animal populations. This improved capability reveals the rapid decline of animal species. We understand the problem, but the crucial question is: how do we implement a solution? Will humanity be capable of extinguish the fire of extinction? Does it have any meaning to expect that nature will heal itself through evolution? How can we persuade decision-makers for the severity of the problem and the solutions needed? As more species face extinction, biodiversity loss worsens. Can we stop the ex-

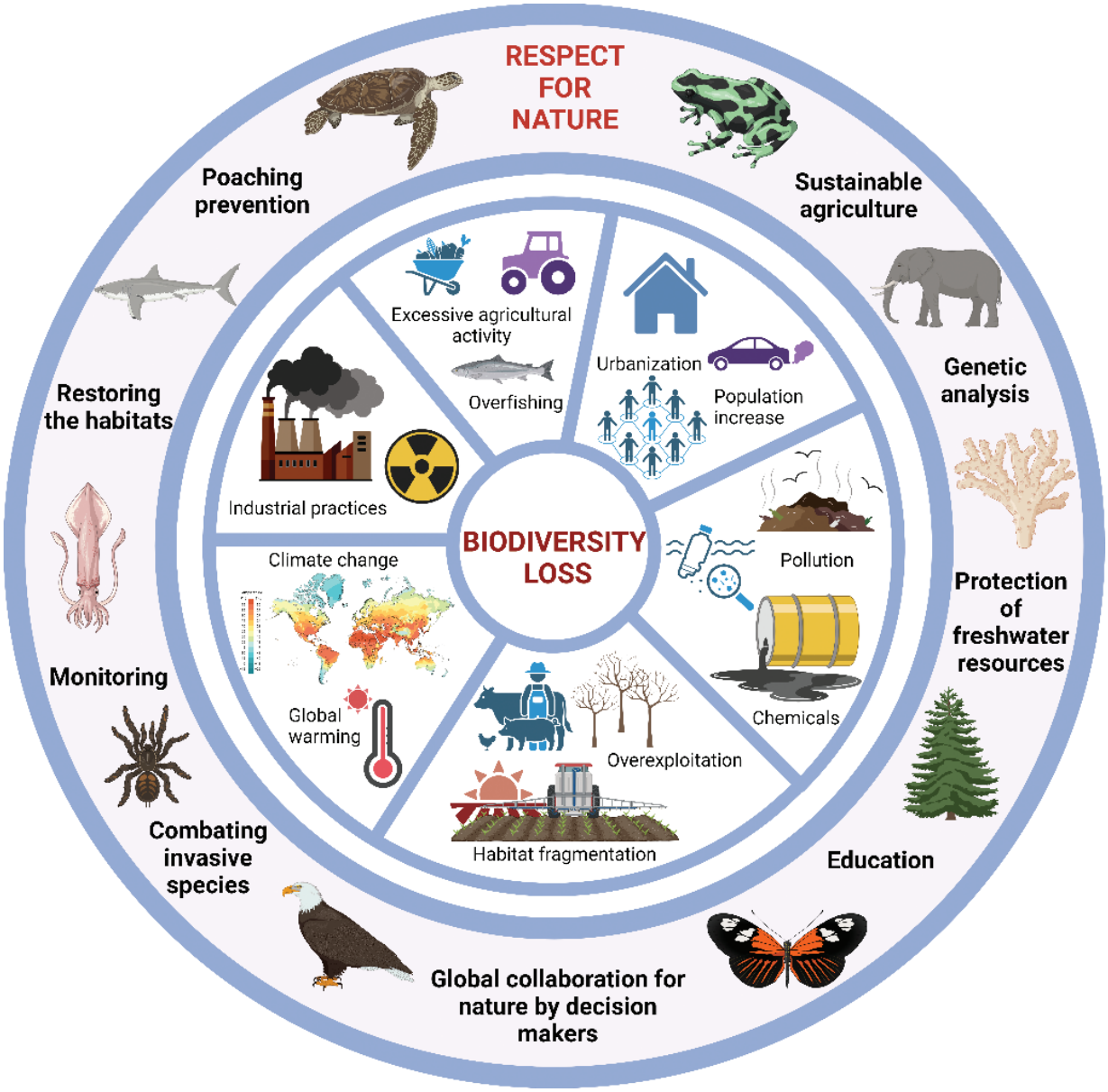

Figure 1 A brief summary of the main factors leading to biodiversity loss and key strategies for conserving biodiversity. Human activities, including but not limited to climate change-induced global warming, habitat fragmentation and degradation, overexploitation of resources, rapid urbanization, unsustainable agricultural practices, overfishing, pollution from various sources, and intensive mining and industrial activities, have significantly impacted natural habitats. As a result, many ecosystems are struggling to support their rich biodiversity. There is an increasing imperative to undertake concerted efforts aimed at safeguarding biodiversity and mitigating human-induced species extinctions. Advancements in technology, such as GPS systems for tracking animal migration routes and genetic studies for species differentiation, have significantly improved the ability to identify and monitor animal populations. Furthermore, artificial insemination, embryo transfer, and, more recently, cloning present promising avenues for species conservation efforts. Essential measures for conserving endangered and threatened species include breeding programs, habitat restoration, and legal protection. These efforts also encompass preserving natural habitats and establishing protected areas to safeguard ecosystems and their associated species. Additionally, promoting sustainable land management practices, such as sustainable agriculture, forestry, and fisheries, helps minimize habitat destruction and preserve biodiversity. Public awareness about the importance of biodiversity conservation should be increased, and sustainable behaviors should be promoted. This approach is indispensable for the comprehensive protection of terrestrial and marine species, spanning from flora to fauna.

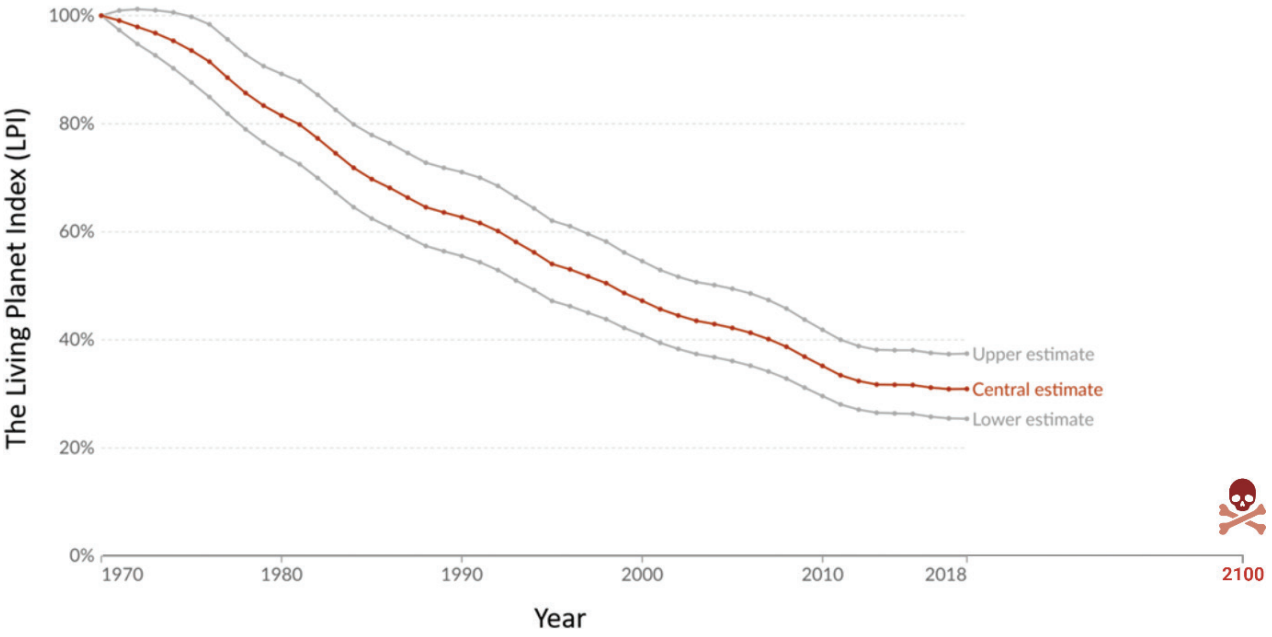

Figure 2 The Living Planet Index (LPI) assesses the average decline in monitored wildlife populations. The index value quantifies the alteration in abundance across 31,821 populations spanning 5,230 species, relative to the baseline year of 1970 (set at 100%). During the period from 1970 to 2018, a segment of these populations witnessed an average decline of 69% in their abundance. These changes have led to significant reductions in wildlife populations, as demonstrated by the LPI, which indicates an average decrease of 60% in species abundance over the last five decades. Based on projections, Southeast Asia is anticipated to adopt characteristics akin to those of a "tropical Europe" by the year 2100. Moreover, the prevailing extinction rate, now doubled in comparison to past assessments, indicates a substantial elevation in extinction occurrences projected for the same period. Particularly susceptible are specific taxonomic groups such as large mammals, forest-associated avifauna, orchids, and butterflies.

tinction of species entirely or only reduce its rate? To address disruptions from human actions like artificial insemination and cloning, we can employ assisted reproductive technologies for species conservation. Financing biodiversity conservation can be achieved through government funding, private partnerships, payments for ecosystem services, biodiversity offsets, and innovative financing mechanisms (Figure 1). As humans, we must find a balanced approach that avoids extremes, respect nature, and avoids harming other living beings when interacting with them, much like how we discovered atom splitting, vaccines, antibiotics, and the smallpox eradication program.

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TABLE 1

Some examples of critically endangered animal species designated as The International Union for Conservation of Nature (IUCN) Red List of Threatened Species (Red Data Book).

Species	Scientific Name
Wild Camel	*Camelus ferus*
Mountain Pygmy Possum	*Burramys parvus*
Addax	*Addax nasomaculatus*
Hirola	*Beatragus hunteri*
Tamaraw	*Bubalus mindorensis*
European Mink	*Mustela lutreola*
Pygmy Raccoon	*Procyon pygmaeus*
African Wild Ass	*Equus africanus*
Riverine Rabbit	*Bunolagus monticularis*
Brown Spider Monkey	*Ateles hybridus*
Red-shanked Douc Langur	*Pygathrix nemaeus*
Chinese Stripe-necked Turtle	*Mauremys sinensis*
Portland Ridge Frog	*Eleutherodactylus cavernicola*
Celebes Crested Macaque	*Macaca nigra*
Pig-tailed Snub-nosed Langur	*Simias concolor*
Tana River Mangabey	*Cercocebus galeritus*
Delacour's Langur	*Trachypithecus delacouri*
San Martin Titi Monkey	*Plecturocebus oenanthe*
Olalla Brothers' Titi	*Plecturocebus olallae*
Black Crested Gibbon	*Nomascus concolor*
Great Hammerhead	*Sphyrna mokarran*
Macedonian Grayling	*Pseudochazara cingovskii*
Siau Island Tarsier	*Tarsius tumpara*
Thongaree's Disc-nosed Bat	*Eudiscoderma thongareeae*
Blue-eyed Black Lemur	*Eulemur flavifrons*
Galápagos Pink Land Iguana	*Conolophus marthae*
Indri	*Indri indri*
Sand Tiger Shark	*Carcharias taurus*
Verreaux's Sifaka	*Propithecus verreauxi*
Mongoose Lemur	*Eulemur mongoz*

The recent data clarifies that the 4,008 species (animalia kingdom) are listed on the IUCN Red List and specifies that the examples provided below are among those classified as critically endangered.

The entire list can be accessed at https://www.iucnredlist.org/search/list?searchType=species&scopes=1&taxonLevel=Species&redListCategory=ex&taxonomies=100041

TABLE 2

Several instances of extinct animal species have been recorded in the last decade, including mammals, birds, fish, insects, and other classes. This trend emphasizes the urgent need to protect global biodiversity from widespread threats.

Species	Scientific Name	Year*
Schomburgk's Deer	*Rucervus schomburgki*	2014
Giant Fosa	*Cryptoprocta spelea*	2015
Sea Mink	*Neovison macrodon*	2015
Pinta Giant Tortoise	*Chelonoidis abingdonii*	2015
Christmas Island Pipistrelle	*Pipistrellus murrayi*	2016
Saudi Gazelle	*Gazella saudiya*	2016
Queen of Sheba's Gazelle	*Gazella bilkis*	2016
Steller's Sea Cow	*Hydrodamalis gigas*	2016
Hispaniolan Edible Rat	*Brotomys voratus*	2016
Oriente Cave Rat	*Boromys offella*	2016
Torre's Cave Rat	*Boromys torrei*	2016
Blue-grey Mouse	*Pseudomys glaucus*	2016
Big-eared Hopping Mouse	*Notomys macrotis*	2016
Long-tailed Hopping Mouse	*Notomys longicaudatus*	2016
Maclear's Rat	*Rattus macleari*	2016
Bulldog Rat	*Rattus nativitatis*	2016
Indo-chinese Warty Pig	*Sus bucculentus*	2016
Red-bellied Gracile opossum	*Cryptonanus ignitus*	2016
White-footed Rabbit Rat	*Conilurus albipes*	2016
Thylacine	*Thylacinus cynocephalus*	2016
Eastern Hare Wallaby	*Lagorchestes leporides*	2016
Kuluwarri	*Lagorchestes asomatus*	2016
Bluebuck	*Hippotragus leucophaeus*	2017
Galapágos Giant Rat	*Megaoryzomys curioi*	2017
St. Vincent Pygmy Rice Rat	*Oligoryzomys victus*	2017
Pemberton's Deer Mouse	*Peromyscus pembertoni*	2017
Desmarest's Pilorie	*Megalomys desmarestii*	2017
Santa Lucian Pilorie	*Megalomys luciae*	2017
Jamaican Rice Rat	*Oryzomys antillarum*	2017
Nelson's Rice Rat	*Oryzomys nelsoni*	2017
Indefatigable Galapagos Mouse	*Nesoryzomys indefessus*	2017
Gould's Mouse	*Pseudomys gouldii*	2017
Edith's Island-shrew	*Nesophontes edithae*	2017
Haitian Nesophontes	*Nesophontes zamicrus*	2017
Western Cuban Nesophontes	*Nesophontes micrus*	2017
St. Michel Nesophontes	*Nesophontes paramicrus*	2017
Atalaye Nesophontes	*Nesophontes hypomicrus*	2017
Greater Cuban Nesophontes	*Nesophontes major*	2017
Floreana Giant Tortoise	*Chelonoidis niger*	2017
Christmas Island Whiptail Skink	*Emoia nativitatis*	2017
Puerto Rican Hutia	*Isolobodon portoricensis*	2018
Imposter Hutia	*Hexolobodon phenax*	2018
The Samaná Hutia	*Plagiodontia ipnaeum*	2018
Little Swan Island Hutia	*Geocapromys thoracatus*	2018
Cuban Coney	*Geocapromys columbianus*	2018
Montane Hutia	*Isolobodon montanus*	2018
Marcano's Solenodon	*Solenodon marcanoi*	2018
Parras Characodon	*Characodon garmani*	2018
Sardinian Pika	*Prolagus sardus*	2019
Darwin's Galápagos Mouse	*Nesoryzomys darwini*	2019
Buhler's Coryphomys	*Coryphomys buehleri*	2019
Lesser Mascarene Flying-fox	*Pteropus subniger*	2019
Vespucci's Rodent	*Noronhomys vespuccii*	2019
Golden Toad	*Incilius periglenes*	2019
Chiriqui Harlequin Frog	*Atelopus chiriquiensis*	2019
Lord Howe Long-eared Bat	*Nyctophilus howensis*	2020
Percy Island Flying Fox	*Pteropus brunneus*	2020
Guam Flying Fox	*Pteropus tokudae*	2020
Jamaican Monkey	*Xenothrix mcgregori*	2021
Large Sloth Lemur	*Palaeopropithecus ingens*	2021
Cheongpung Blind-beetle	*Coreoblemus parvicollis*	2022
Campo Grande Treefrog	*Boana cymbalum*	2023
Thick-billed Ground-dove	*Pampusana salamonis*	2023
Oceanic Parrot	*Eclectus infectus*	2023
Aurochs	*Bos primigenius*	2023
Raiatea Parakeet	*Cyanoramphus ulietanus*	2023
Paradise Parrot	*Psephotellus pulcherrimus*	2023
Pagan Reed-warbler	*Acrocephalus yamashinae*	2023
Cheongpung Blind-beetle	*Coreoblemus parvicollis*	2023

** Extinction year*

The entire list can be accessed at https://www.iucnredlist.org/search?searchType=species&scopes=1&taxonLevel=Species&redListCategory=ex&taxonomies=100041

6 EDUCATION FOR ACHIEVING PLANETARY HEALTH

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KEY MESSAGES

- Planetary health education is crucial to address the intertwined challenges of poverty, health inequity, and environmental degradation
- Enhancing planetary health literacy among diverse stakeholders can foster informed decision-making across multiple settings
- Integrating climate and health education into all curricula, especially for girls and women, is a necessary foundation for personal and public health
- Comprehensive training on climate-related health conditions is imperative for public health and healthcare professionals
- A holistic, interdisciplinary approach to climate change and health education is needed to address the complex challenges of planetary health
- Collaborations between science-based organizations and frontline community groups are key to educating the public and building resilient communities

The imperative for planetary health education stems from the urgent need to confront the intertwined challenges of poverty, health inequity, and environmental degradation. Education serves as the cornerstone for overcoming these barriers, empowering individuals to navigate complexities and advocate for solutions.

Informing people about the health effects of global warming can increase public engagement and reduce political polarization on the issue.

By enhancing planetary health literacy among various stakeholders and catering to diverse needs across regions and sectors, we can foster informed decision-making in multiple settings. From early childhood education to pre-professional training, integrating climate and health education into curricula, especially for girls and women, is a necessary foundation for personal and public health. As students progress through their education, opportunities for experiential learning and interdisciplinary approaches can deepen their understanding of climate-health intersections.

For public health and healthcare professionals, comprehensive training on climate-related health conditions is imperative. Healthcare professionals must be equipped to recognize, treat, and prevent climate-related health conditions. Initiatives like the Sustainable Healthcare Education Network and the Global Consortium on Climate and Health Education are instrumental in setting educational goals and competencies (Table 1). In addition, The Nurses Climate Challenge empowers nurses to provide education about the health impacts of climate change.

Institutions and organizations worldwide are beginning to recognize the urgency of incorporating climate change and health equity into medical and nursing curricula, mostly because of grassroots efforts by students. However, significant challenges remain, including resource constraints and curriculum saturation. Overcoming these barriers requires top-down mandates, collaborative efforts, and innovative approaches to curriculum development (Figure 1).

TABLE 1

Global Consortium on Climate and Health Education Core Competencies	
Competencies for all Health Professions	
Domain	**Unit of Competency**
Knowledge and Analytical Skills	• Define climate drivers (both natural and human-caused), weather, climate change, and climate variability. • Identify the health impacts of climate change and effective responses on the part of specific health services. • Apply knowledge of levels of prevention, climate mitigation and adaptation, and explain health co-benefits of actions. • Describe public health and its determinants. • Apply knowledge of emergency planning skills. • Access and interpret relevant local, regional, national, and global information about climate change effects on health. • Apply knowledge of the ethical, professional, and legal obligations relevant to climate and health. • Demonstrate understanding of the scientific consensus on climate change and concept of evolving science.
Communication and Collaboration	• Demonstrate effective communication with stakeholders about climate and health topics. • Work collaboratively and across disciplines on climate and health issues.
Policy	• Explain the role of subnational, national and global policy frameworks and governance structures to address health risks associated with climate change. • Explain climate-health activism and policy engagement roles of health professionals.
Public Health Practice Competencies	
• Apply climate and health knowledge to improve decisions about public health services, and adapt and improve population health. • Apply knowledge of the connection between habitat and biodiversity loss and infectious diseases.	
Clinical Practice Competencies	
• Describe ways that healthcare professionals and facilities can prepare for and respond to climate–related health risks. • Apply knowledge of climate and health to clinical care of patients.	

A holistic approach to climate change and health education, encompassing fields beyond healthcare, is needed to address the complex challenges of planetary health. Interdisciplinary perspectives such as One Health, EcoHealth, and Planetary Health offer comprehensive frameworks for understanding the interconnectedness of human health and the environment.

While progress has been made in planetary health education there are still significant gaps, particularly in low-income countries and among indigenous communities. Education plays a crucial role in empowering communities to respond to climate-related health threats. Collaborations between science-based organizations and frontline community groups are key to educating the public to drive collective action and build resilient communities.

In conclusion, education is indispensable for achieving planetary health. By equipping individuals with the knowledge and skills to address climate-related health challenges, we can catalyze transformative change and create a healthier, more sustainable future for all.

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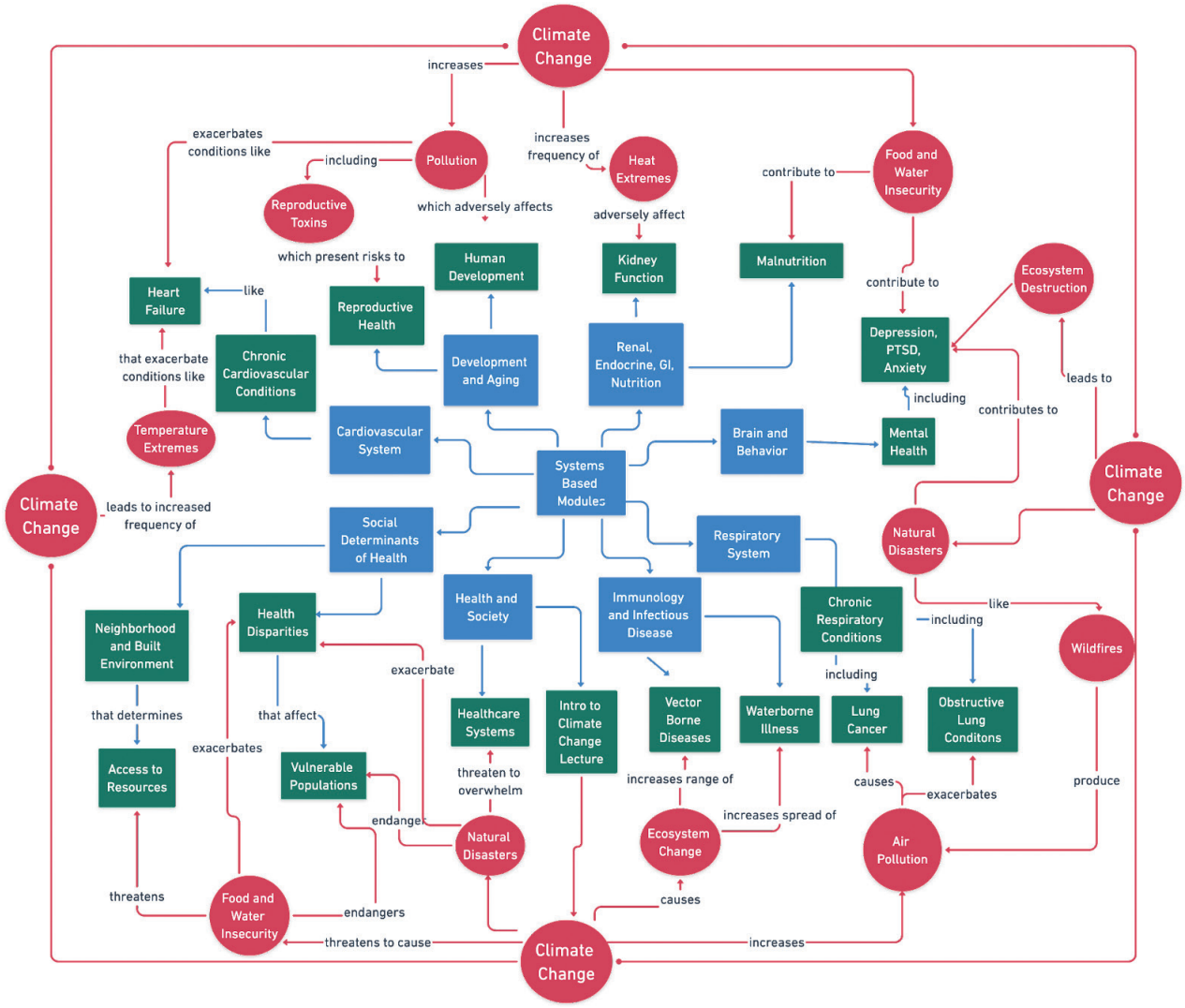

Figure 1 Example medical school climate change and health curricular map, demonstrating the intersections between climate change and organ-system-based preclinical content (adapted from Ndovu et al). (Ndovu A, Sirias T, Whelan H, Iverson N. CHASE Concept Map. 2019)

7 EPITHELIAL BARRIER THEORY AND SUGGESTIONS TO PATIENTS

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KEY MESSAGES

- Specific recommendations to patients are general recommendations, and epithelial barrier-specific recommendations for skin, gut and mucosal barriers
- General recommendations include raising of awareness on barrier and microbiome toxic environmental substances, avoidence of allergens and barrier toxic substances, and stress management
- Skin care, dietary considerations and mucosal protection are major areas that need future research and improvements

INTRODUCTION

There is a major, currently unmet need to translate the recent discoveries on the link between epithelial barrier damage and various diseases into our clinical practice. Here below are a series of recommendations that we can and should inform to patients and lay public based on our current knowledge. There is a huge amount of ongoing research in the area and many more suggestions to facilitate the avoidance of exposure and mitigation of the epithelial barrier damaging effects are expected to be proposed in the near future.

GENERAL RECOMMENDATIONS

Overall, we should **raise awareness** about the epithelial barrier theory, how it may impact our health and promote the emergence of some diseases (Table 1).

Awareness of environmental factors: We can help our patients realize how environmental factors may compromise their health via their action on epithelial barriers. This includes aerogenic exposure to air pollution, cigarette smoke, ozone. It includes exposure (via ingestion) of microplastics, and skin exposure to chemicals contained in detergents and cleaning agents. We should suggest limiting exposure to these elements as much as possible.

Avoidence of epithelial barrier toxic substance exposure: There is a number of epithelial barrier toxic substances listed in text box 1. It is possible to avoid the exposure to many of these substances in laundry, dishwashers and cleaning products, toothpastes, packaged food, indoor and outdoor pollutants.

Avoidance of allergen exposure: This is already part of our basic recommendations. Patients should as strictly as possible avoid allergens known as triggers of their allergic conditions (i.e. allergic asthma, rhinitis, food allergy and allergic contact dermatitis) Repeated allergen exposure exacerbates barrier disruption and allergic inflammation.

Stress management: We explain our patients how stress can influence inflammation and epithelial barrier integrity. We can suggest strategies for stress management, which however are patient-dependent. These may include a good sleep hygiene, regular exercise, and relaxation techniques.

RECOMMENDATIONS FOR THE PROTECTION OF A HEALTHY MICROBIOME AND ITS BIODIVERSITY

Epithelial "Barrier-specific" recommendations:

Skin. Skin care: Especially in patients with atopic dermatitis, but

TABLE 1

General recommendations		
Awareness of environmental factors	Objective	Minimize exposure to harmful environmental factors
	Actions	• Avoid aerogenic exposure to pollutants (air pollution, cigarette smoke, ozone) • Limit ingestion of microplastics • Reduce skin exposure to harsh chemicals (detergents, cleaning agents)
Avoidance of Barrier Opening Toxic Substances	Objective	Decreasing the publicly exposed dose or fully avoiding toxic substances
	Actions	• Demonstration of the toxic dose threshold • Discovery of less toxic substances with a similar performance • Reinforcing regulatory authorities and academia for environment monitoring
Avoidence of Allergen Exposure	Objective	Contribute to avoiding exacerbations and chronicity
	Actions	• Avoid causative allergens
Stress Management	Objective	Reduce stress
	Actions	• Implement stress-reduction strategies tailored to individual needs (sleep hygiene, regular exercise, and relaxation techniques)

also with allergic or irritant contact dermatitis, we should emphasize the importance of a basic skin care regimen. We should recommend avoiding strong sanitizers, and frequent hand washing with harsh soaps and desinfectants. Patients should favor hypoallergenic, fragrance-free emollients. Products containing e.g. ceramides may support epidermal barrier in particular.

Gut. Dietary considerations: We can discuss with our patients the potential impact of diet on the gut epithelial barrier. We should advise avoiding foods rich in antibacterial and antifungal additives, artificial emulsifiers and processed foods. We may encourage a diet rich in fibers and whole foods, natural products, that supports a healthy gut microbiome, in the context of a healthy anti-inflammatory diet, which is generally recommended for many chronic inflammatory conditions. Recommendations on the use of probiotics may require a disease-specific assessment.

Mucosal barriers. Humidification and hydration: We may recommend patients with airway diseases using a humidifier if needed to help keep mucosal barriers such as those in the nose, throat, and airways humid and thus protected, especially in dry environments.

CONCLUSION

Taken together, we should empower patients to take proactive steps in "promoting epithelial barrier health". We need to establish science- and evidence-based approaches targeting the different facets of epithelial barrier damage in our patients.

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8 THE ROLE AND RESPONSIBILITY OF SCIENTIFIC ORGANIZATIONS

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KEY MESSAGES

- EAACI disseminates evidence on planetary health in all congresses and scientific events
- EAACI generates position papers and guidelines to educate professionals on planetary health
- EAACI promotes the inclusion of planetary health in the training curricula of Allergy specialists
- EAACI organizes lobbying activities at European institutions to raise awareness about planetary health, in strategic partnerships with patients' organizations

Scientific organizations like EAACI are placed in a unique position to help mitigate the deleterious consequences of outdoor pollution and climate change over asthma and allergic diseases. On the one hand, they organize top-quality scientific events where novel data and established evidence is disseminated to an expert audience. In this regard, the EAACI regularly includes sessions on respiratory health, pollution and global warming in its main congresses and meetings, whereas it also organizes specific events focused on environmental science. Moreover, the EAACI has done a great effort to develop good quality material on planetary health to be displayed in educational online platforms like the Knowledge Hub. Thus, EAACI members can access this material on demand, and get trained on the deleterious impact of pollution on human health. Besides science dissemination, societies can also generate top quality scientific documents which educate the medical and research community on the twin epidemics of endangered planetary health, and asthma and allergic diseases. EAACI sections, interest groups and working groups publish regularly position papers on this issue, and elaborate guidelines including state-of-the art systematic reviews. A good example of this are EAACI Guidelines on Environmental Science, which have provided top quality evidence on the effect of outdoor pollution and extreme temperatures on asthma outcomes (Figure 1). To facilitate these tasks, EAACI has also created a working group specifically focused on "One Health", whereas pollution and climate change are always present in the core activities of the rest of sections, interest groups and working groups. Scientific societies are recognized as reference bodies not only by clinicians and researchers, but also by patients' organizations, regulatory agencies and policymakers. For example, EAACI provides guidance to develop proper training curricula for Allergy specialists. In this regard, EAACI strongly supports the education of clinicians on how to evaluate the patient's exposome, and how to implement preventive measures for outdoor and indoor pollution. Scientific societies have a unique opportunity to raise awareness about risk factors for unfavorable health outcomes among the general population, in addition to promote the necessary legal and regulatory changes to mitigate the burden of chronic diseases. In this regard, EAACI is a founder member of the Interest Group on Asthma and Allergic Diseases at the European Parliament. Through this group and together with the patients' representatives, EAACI organizes regularly lobby-

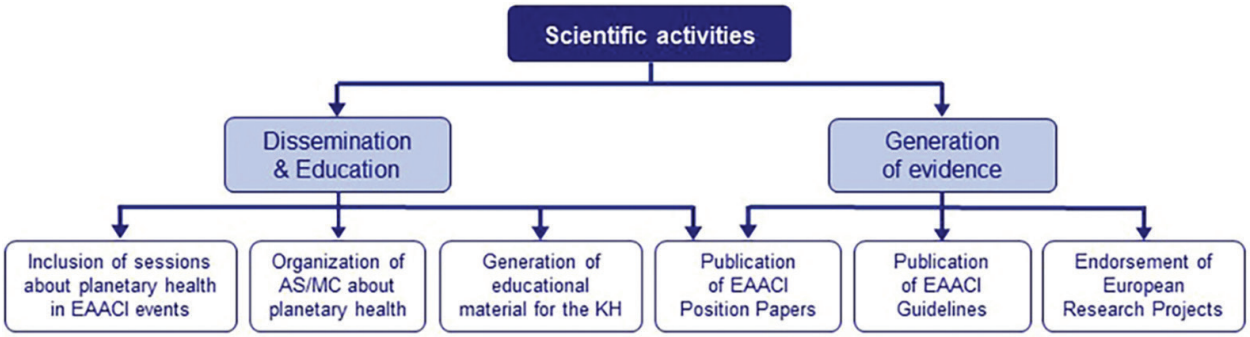

Figure 1 Scientific activities that are developed by EAACI to help mitigate the deleterious impact of pollution and climate change on allergic diseases and asthma. AS: Allergy School; KH: Knowledge Hub; MC: Master Class.

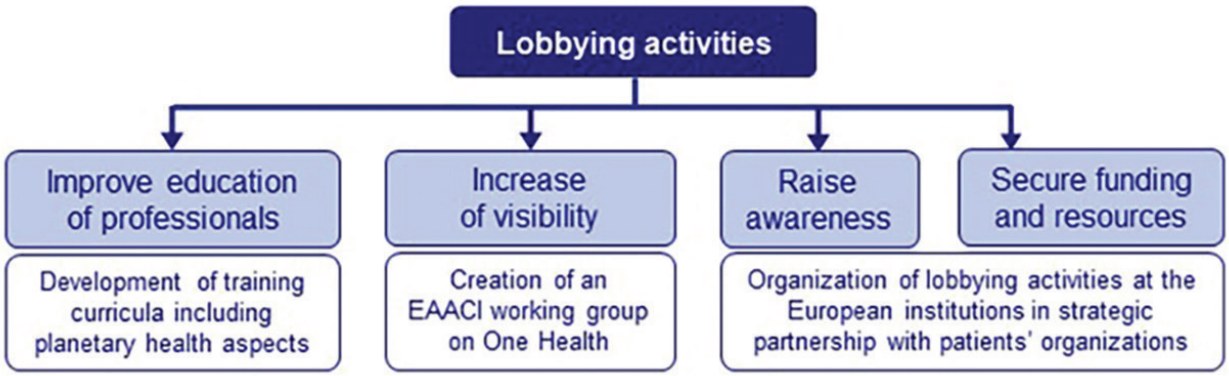

Figure 2 Lobbying activities that are developed by EAACI to help mitigate the deleterious impact of pollution and climate change on allergic diseases and asthma

ing and disease awareness activities at the European institutions, in order to ensure that enough funding and resources are allocated for research and the healthcare of patients with allergic diseases and asthma. These events also address the need to implement legal changes to limit the burden of outdoor pollution, speed down the raise of global temperatures, and subsequently decrease the severity, mortality rate and prevalence of asthma and other allergic diseases (Figure 2).

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9 PATIENT ADVOCACY

Tonya Winders
Global Allergy & Airways Patient Platform

Healthy people require a healthy planet to live free from the burden of atopic and airways diseases.

Climate change, loss of biodiversity, pollution, heat stress, extreme weather events and a lack of access to care all worsened by health inequities are major concerns for the one billion people living with these conditions. Patient advocacy organizations (PAGs) are often at the forefront of these issues striving to empower people to live without impairment.

KEY MESSAGES

- Patient advocacy groups drive awareness of planetary health in respiratory health
- Patient advocacy groups educate patients and providers on the importance of climate and health
- Patient advocacy groups advocate to governments on behalf of patients to ensure a healthy planet and healthy patient coexist

First, PAGs drive awareness of the impact of planetary health on chronic conditions like asthma, COPD and more. For example, climate change and extreme weather events result in longer, stronger pollen seasons which can result in more severe symptoms for those living with allergic asthma.

Moreover, PAGs develop educational programs for patients, carers, healthcare professionals and policymakers to reinforce the importance of indoor and outdoor air quality for conditions like asthma, COPD and other lung conditions. These initiatives offer pragmatic approaches to mitigate risks.

PAGs also engage policymakers at local, national, regional & global levels to prioritize planetary health policies.

Examples include:

Local. Asthma Lung UK campaigns for the community to use public transportation, walking/cycling and no idling zones for fewer carbon emissions.

National. Allergienet in Belgium educates the community on the importance of climate change and air quality.

Regional. EFA is instrumental in F-Gas regulatory changes to reduce emissions from inhalers.

Global. GAAPP advocates with WHO to advance SDG 2030 and a member of the International Respiratory Coalition Steering Committee leading 19 national coalitions to elevate lung health.

Finally, PAGs often engage in research projects to understand patient beliefs and behaviors regarding planetary health and environmental sustainability. It is vital to include these perceptions in the medical and policy literature to gain a better understanding & ensure adoption of best practices to improve outcomes.

In conclusion, PAGs are an essential partner to drive awareness, educate stakeholders, advocate for meaningful change and research innovative ways to effect positive change in the war to save our planet and our immune/lung health.

10 THE ROLE AND RESPONSIBILITY OF PATIENT ORGANISATIONS

Özlem Ceylan
EAACI Patient Organisations Committee Chair

KEY MESSAGES

- Through advocacy efforts, patient organisations can influence policies and practices that promote environmental sustainability and protect natural resources
- Patient organisations can participate in research exploring the connections between environmental factors and human health outcomes, generating evidence-based recommendations for action
- On a global level, they can use their expertise, share best practices, and advocate for policies that address environmental justice and ensure equitable access to healthcare services

In recent years, the concept of planetary health has garnered growing recognition and importance, emphasizing the interconnections between the well-being of the planet and its inhabitants. While governments, policymakers, and researchers play crucial roles in advancing planetary health goals, patient organisations also hold a unique and critical role in this global endeavour.

RAISING AWARENESS AND ADVOCACY

Patient organisations are instrumental in raising awareness about the impact of environmental factors on health. They educate their members and the public about the links between environmental degradation and human health. They can provide educational resources to help individuals make environmentally conscious choices and adopt eco-friendly lifestyles. They can also lead by example by adopting sustainable practices in their operations; such as reducing waste, conserving energy, and promoting digital transformation.

SUPPORTING VULNERABLE POPULATIONS

Patient organisations focus on supporting vulnerable populations, including immunocompromised individuals and patients with climate-sensitive diseases. They provide support and resources for communities facing health challenges exacerbated by environmental factors, such as air pollution, prolonged aeroallergen seasons and climate-related disasters. As primary actors in emergency preparedness and response, they can disseminate warnings and action plans to facilitate community resilience.

BUILDING PARTNERSHIPS AND COLLABORATION

Collaboration is key to addressing the complex challenges of planetary health, and patient organisations are adept at building partnerships across sectors. They collaborate with healthcare providers, researchers, policymakers, public health agencies, government bodies and environmental organisations to develop holistic approaches to health and environmental issues. They can support and participate in research on the health effects of environmental factors, such as air and water pollution, climate change, and exposure to chemicals.

PROMOTING SUSTAINABLE HEALTHCARE PRACTICES

Patient organisations also play a role in promoting sustainable healthcare practices that minimize environmental impact. By promoting disease prevention, early

diagnosis, personalised medicine, e-health and telemedicine; patient organisations contribute to reducing the healthcare sector's environmental footprint which currently on average accounts for 5% of the national carbon footprint, making the sector comparable in importance to the food sector.

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11 PLANETARY HEALTH REQUIRES INTEGRATED APPROACHES FOR FLOURISHING AT ALL SCALES

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"From common risks to common opportunities, a more united global agenda must align planetary and human health targets, and their translation"

Human disruptions to Earth's natural systems, are directly damaging to all life, including our own. Large-scale industrialization threatens the health of water, air, soil, and food systems, and is directly implicated in mass biodiversity losses including dysbiosis at foundational microecological scales. Rising rates of disease, distress, and despair are inextricably linked with destruction of these interdependent ecosystems. The pandemic of chronic, noncommunicable diseases, including allergic diseases, reflects these deepening imbalances, which are manifest at the cellular level with rising lifelong propensity for inflammation. Overcoming these grand challenges requires deep structural changes in how we live.

Solutions will depend on simultaneous attention to enmeshed ecological challenges to well-being - including the upstream social, economic, and political 'ecosystems' that are undermining flourishing. These must address the value systems guiding human actions, with deep understanding of the complex interdependence of all systems, and cross-sectoral collaboration to ensure integrated solutions that promote flourishing for all (Figure 1). It calls for kinder, more compassionate co-beneficial approaches with a transgenerational vision that moves beyond the territorial, siloed thinking that currently hampers progress (Figure 2).

The Planetary Health framework offers a solutions-orientated holistic perspective of ecological interdependence that connects the health and vitality of individuals, communities, and Earth's natural systems. It also encompasses human-made social, political, and economic systems that influence attitudes, values, and behaviors - of individuals and whole societies.

The Planetary Health Alliance (PHA), a growing global consortium of over 400 universities, non-governmental organizations, and government entities, defines planetary health as "*a solutions-oriented, transdisciplinary field and social movement focused on analyzing and addressing the impacts of human disruptions to Earth's natural systems on human health and all life on Earth*".

KEY MESSAGES

- Large-scale human activity in the Anthropocene has disrupted ecological balance in virtually all systems, from the planetary to the personal scale, and is implicated in the rising rates of chronic inflammatory disease and premature death
- To address these interconnected threats to well-being at all scales, the planetary health agenda provides a framework for integrated co-beneficial solutions, cross-sectoral collaboration, and social movements aimed at mutual flourishing of all human and natural systems
- Human flourishing depends on the health of our natural, built, and social environments, and the systems and structures that support well-being, symbiosis, balance, and mutualism in every sense - including the value systems and worldviews that determine attitudes and actions

This framework encourages unified systems approaches and provides a vision for cross-sectoral collaboration, including greater engagement with social sciences, the arts, and humanities. It underscores the need for more mutualistic strategies that address the policies and practices (and the attitudes and values that govern these) for solutions that provide co-benefits for "people, places, and planet". This is reflected in the 2022 WHO health policy brief which emphasizes a whole-of-society approach, spanning from the planetary to the individual scale, giving attention to societal values and life-course approaches. This expansion from public to planetary health requires wider

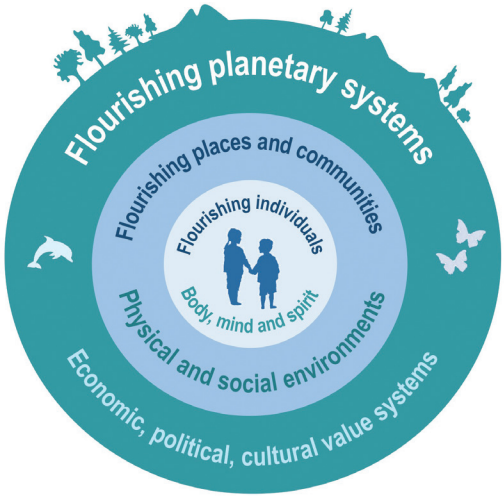

Figure 1 A laudable goal: flourishing as more than the absence of disease: equitable flourishing and fulfillment of individuals requires societies, systems and values that promote mutual flourishing. It also depends on overcoming the systemic factors that undermine this, recognizing the interconnected ways these influence the wellbeing of people, places, and planet.

Figure 2 Planetary Health Requires Tapestry Thinking: Overcoming siloed thinking for meaningful integration requires a cultural shift as a precondition for structural change. Combining and aligning efforts can also amplify awareness, advocacy, and action towards wiser and more effective solutions.

Figure 3 Healing the relationship crisis between humans and nature: Solutions must address the worldviews, ethics and values that elevate 'profit and power' over 'people and planet', and extractive mindsets as root causes of social and ecological injustice.

systems integration, built upon on principles of social and ecological justice, which directly connect personal wellbeing with wellbeing of all systems at scale.

Fundamentally, the principles of planetary health follow the wisdom and knowledge systems of Indigenous peoples handed down over millennia: "*to harm the Earth is to harm the self*". Therefore, in addition to considering the vital biophysical "planetary boundaries" needed to support human flourishing, planetary health also considers the mindsets and the worldviews that created and perpetuate our global challenges—including calls to address structural inequalities, injustices, and the social, emotional, and spiritual dimensions of unrealized human potential (Figure 3). This requires for more integrated approaches to research and policy, and educational frameworks that promote emotional intelligence, moral wisdom, and cultural capacities to ensure human flourishing and flourishing planetary systems.

"*I used to think the top global environmental problems were biodiversity loss, ecosystem collapse and climate change. I thought that with 30 years of good science we could address these problems. But I was wrong. The top environmental problems are selfishness, greed and apathy, and to deal with these we need a spiritual and cultural transformation, and we lawyers and scientists don't know how to do that.*" Environmental lawyer, James Gustave "Gus" Speth, 2013

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